The Nation's Investment in Cancer Research
A Plan and Budget Proposal for Fiscal Year 2003

Review Draft
July 2001

Please submit your questions, comments, and suggestions by August 13th to:

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
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July 23, 2001

Dear Colleague:

The National Cancer Institute's (NCI) annual strategic plan and budget document, *The Nation's Investment in Cancer Research*, serves as a focal point for prioritizing the efforts of NCI and a reference for cancer research planning by other organizations. It is a document used to communicate our vision, goals, and plans not only to the President and Congress but also to NCI staff, the research community, professional organizations, cancer advocacy groups, foundations, and others interested in working together to support cancer research.

Currently we are developing our Fiscal Year 2003 document, and I am once again asking for your review and suggestions. We need your ideas for articulating the value of our investments to date, showing how focused efforts through our Extraordinary Opportunity and NCI Challenge areas will continue to accelerate the pace of discovery, and helping readers understand the difference all of this will make in the lives of people.

Your comments and suggestions are very important to us, and we will carefully consider your input as we complete our final editing during the month of August. We are running a bit behind in sending out this review draft, but we will need your comments no later than Monday, August 13th.

Please submit your comments to Cherie Nichols (nicholsc@mail.nih.gov) or Kathie Reed (reedk@mail.nih.gov) by email or mail them to the address on the first page of this document. If you have questions, please email Ms. Nichols or Ms. Reed or telephone our Office of Science Planning and Assessment at 301/496-5515.

Thank you very much for your help.

Sincerely,

Richard D. Klausner, M.D.
Director, National Cancer Institute

Attachment: Draft text for *The Nation's Investment in Cancer Research:*
A Plan and Budget Proposal for Fiscal Year 2003

The Nation's Investment in Cancer Research
NCI's Plan and Budget Proposal for 2003

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Our Role in Cancer Research

The National Cancer Institute's overall mission and goal is to *stimulate and support scientific discovery and its application to achieve a future when all cancers are uncommon and easily treated.*

NCI works toward this goal by providing vision to the Nation and leadership for thousands of NCI-funded researchers across the United States and around the world and working to assure that the results of research are translated into reducing the burden of all cancers for all people. We:

- Conduct, coordinate, and support cutting-edge research and its application.
- Build upon past discoveries and promote creativity and innovation.
- Support development of, access to, and use of new technologies.
- Disseminate cancer information to our many communities.
- Support training and career development for cancer researchers.
- Facilitate the movement of research findings into clinical practice.
- Maintain support mechanisms and collaborative environments to link scientists with their colleagues and with critical technological and information resources.
- Develop strategies to define, improve measure, and monitor the quality of cancer prevention and care and reduce disparities in outcomes.

Our work is driven by careful planning and priority setting. This includes:

- **Defining and building a research infrastructure.** We give priority to developing the technological and personnel resources needed to support changing scientific and resource needs and the translation of new knowledge and emerging technologies into clinical practice.
- **Identifying extraordinary scientific opportunities.** We seek opportunities that promise to provide profound insights into cancer – those opportunities that hold greatest potential to lead to major improvements in our ability to prevent, control, detect, diagnose, and treat cancer.
- **Planning national agendas for disease-specific research.** We continually assess our portfolios and plan for the research needed to uncover the biological characteristics that are unique to specific forms of cancer.

Our success in these endeavors depends on:

- **A superb workforce both inside and outside the Institute.** The competence, hard work, and dedication of our researchers and clinicians and those who support their efforts each day drive our success in discovery and innovation.
- **Insight and advice from those who know and care most about cancer.** We look to representatives from a broad spectrum of scientific, medical, and advocacy

communities in several ways:

- Members of standing and special advisory groups assist us in planning for and evaluating cancer research from conceptual beginnings through clinical application.
- Many people aid us in identifying, planning for, and implementing our "extraordinary opportunities for investment."
- People with diverse perspectives help us plan national agendas in disease-specific research through our Progress Review Groups.

How We Work - to be added

Brief description of how NCI carries out its role

Budget Request for 2003 - to be added

Tables and graphs to show actual and projected budgets along with 2003 request

NCI's Challenge

We are entering the 21st century with ever-expanding knowledge and an array of sophisticated tools for continuing the fight against cancer. The challenge before NCI is to build and continually enhance an infrastructure that will allow the scientific community to apply new discoveries and emerging technologies. We need mechanisms that will promote and reward innovative thinking, the cross-fertilization of ideas among disparate scientific disciplines, and enhanced collaborations among government, academia, and industry. We must develop and maintain a cadre of trained scientists from a variety of disciplines. And we must address special societal concerns and other barriers that jeopardize our Nation's ability to provide the best possible treatment to cancer patients, ensure equal access to information and care, and offer current and future scientists sufficient opportunities to obtain research funding and other kinds of support.

NCI must provide the vision, creative environments, and diverse resources needed to ensure an easy flow between the increasing number of discoveries and advances in cancer research and the scientific community's ability translate these findings into clinical application. If the pace of discovery can be likened to speeding down a superhighway, our current ability to apply these findings still is much like bumping along a country road. Where the two intersect, a bottleneck prevents a tremendous number of good ideas from moving forward. Our challenge is to continue to expand and smooth the country road, hastening discoveries to their application in interventions across the continuum of cancer care – from prevention and early detection to diagnosis, treatment, life after cancer, and the end of life.

To respond to this challenge, we identified six key areas for investment in our 2001 and 2002 proposals and will continue addressing these in 2003. Beginning with our 2002 proposal, we added two new challenge areas to address two persistent barriers to meeting our challenge: (1) the inadequate quality of cancer care and (2) disparities in access to information, patient care, and research opportunities and careers.

Investigator-Initiated Research

The Challenge

Investigator-initiated research – projects conceived by individual researchers and funded through grants – have always been the principal source of advances in biomedical research. Because of the importance of investigator-initiated research, NCI devotes more resources to it than to any other area of its budget.

Making inroads against cancer requires the development of a variety of approaches and technologies. Recent advances, such as the sequence of the human genome, new technologies for identifying molecular targets within cancer cells, and methods for discovering and analyzing promising drugs aimed at each cancer-causing pathway, have provided scientists with a wider arsenal of technologies for research than ever before. However, the use of more sophisticated approaches requires both more resources and a broader variety of options and opportunities for performing research. This is NCI's challenge in the area of investigator-initiated research.

As a consequence, NCI has seen an enormous increase in the need for resources and funding to allow scientists to fully exploit the new technologies. In Fiscal Year 2001, for example, the cost of research projects supported by NCI was nearly 15 percent higher than the year before. In response to this trend, we inevitably are forced to make some compromises in order to balance the growing number of research opportunities with the rising costs of research.

In practice, this need to balance expanding opportunities and increasing costs has forced NCI to support fewer research proposals than are endorsed by peer review and to support each at a lower level than recommended. Though reviewers' assessments of the research proposals we receive consistently identify the top 35 percent to 40 percent of applications as particularly worthy of support, the proportion of research proposals actually funded (the success rate) has averaged only 28 percent in recent years. Moreover, NCI has been able to maintain this success rate only by reducing budgets an average of 15 percent. A lack of funds – rather than a lack of exceptional ideas – remains a significant bottleneck in our fight against cancer.

Low success rates and less than optimal funding may prevent some of the brightest minds of the next generation from choosing to enter cancer research. . But a sufficient infusion of resources and funding into investigator-initiated research opportunities will help to ensure that young people, as well as current researchers, will perceive cancer research as an appealing and rewarding career.

Progress Toward Meeting the Challenge

NCI has sought to enhance careers in cancer research and ensure that progress against cancer will proceed through a variety of policy decisions and flexible funding options.

Identifying and Supporting High-Priority Research

NCI takes extra steps to identify and support high-priority research by:

- Seeking out and supporting compelling research proposals that may have been overlooked in peer review, particularly those suggesting dramatically new or unconventional approaches to understanding cancer

- Giving special consideration to proposals from new investigators, clinical researchers, and those who respond to NCI announcements of priority research areas, such as recommendations from Progress Review Groups for research related to specific cancers

Maximizing the Pace of Discovery

NCI seeks to maximize the pace of discovery by providing a broad range of flexible funding options and promoting collaborations and resource sharing wherever possible:

- Providing opportunities for collaborative study through awards such as program project grants (P01s) and cooperative agreements, in addition to the traditional research project grants (R01s) that make up the bulk of NCI's research portfolio.

- Expanding the use of award mechanisms that provide seed funds for promising research. In Fiscal Year 2000, the number of small (R03) and exploratory/developmental (R21, R33) grants awarded increased more than 25 percent over the previous year.

- Making "administrative supplement" funds available to investigators to allow them to take advantage of unanticipated opportunities or to pursue interdisciplinary collaborations. For example, through NCI's Activities to Promote Research Collaborations Program, investigators can apply for supplements for collaborations to initiate novel research, share resources, develop new technologies, or organize cross-disciplinary meetings or workshops.

- Promoting collaborative studies and sharing of resources through various networks and consortia. (Cross reference to the Centers, Networks, and Consortia Challenge, and others.)

Reviewing Research Proposals Better and Faster

We review grant applications more effectively and make awards more rapidly than in the past. This is possible in large part because of changes such as:

- The establishment of a clinical oncology study section in April 2000 by NIH's Center for Scientific Review, to ensure that applications for clinical research are reviewed by those familiar with the special issues related to such research.

- Electronic approval of grant applications by National Cancer Advisory Board members between their regularly scheduled meetings, permitting Institute staff to notify recipients earlier and, in many cases, allowing research projects to begin sooner than anticipated. This new procedure reduces the standard nine-month funding cycle by more than a month for most applications.

The Plan - Investigator-Initiated Research

Goal

Speed the rate of cancer research discovery, and accelerate the application of discoveries to the population by expanding and facilitating access to resources and new technologies.

Objectives and Milestones for Fiscal Year 2003

1. **Increase the pace of discovery through increased funding for and larger numbers of competing research grants.**

- Support awarded applications at the full levels recommended by peer reviewers.
- Fund, at a minimum, the top 35 percent of competing applications with (1) the highest scientific merit, (2) a less certain probability of success but potential to yield greater reward if they do succeed, (3) unconventional approaches but unique promise, (4) a focus on areas of extraordinary need in specific fields of investigation or model systems, or (5) the involvement of new investigators.

2. **Encourage investigators to commit to careers in cancer research and to propose more innovative and higher reward projects.**

- Continue to allocate the first 80 percent to 90 percent of available funds for research project grants to competing applications that fall within conventional merit rank order paylines, while ensuring that applications from new investigators have a success rate comparable to those from more established investigators.
- Use exceptions funding to support applications that fall outside rank order paylines and that are particularly innovative and/or of high risk but potentially high reward.

3. Facilitate rapid movement from discovery to application by using established mechanisms and creating novel special awards to encourage transdisciplinary and collaborative research.

- Expand administrative supplements to promote new interdisciplinary collaborations that bring together basic and clinical scientists, such as those fostered by NCI's Activities to Promote Research Collaborations Program.
- Expand researcher access to central resources such as databases, tissue banks, and animal models, using administrative supplements; centers, networks, and consortia; and cooperative resource programs.
- Expand researcher access to technologies that promote interdisciplinary research and collaborations and to the expertise needed to move discoveries to application.
- Encourage the development of information technology tools to foster and enhance interdisciplinary communication and collaboration.
- Double the funding for collaborative research awards such as program project grants and cooperative agreements for networks in cancer genetics, imaging, early detection, and other areas.
- Expand the use of exploratory grants to encourage more patient- and population-based research.
- Let peer review be the primary determinant of appropriate funding levels for individual awards.

4. Use regular and special award mechanisms to encourage investigation in priority areas identified by NCI staff, progress review groups, extraordinary opportunity working groups, and advisory committees.

- Monitor investigator-initiated research applications to assess whether these projects alone are meeting programmatic objectives, including those focused on special needs identified in specific disease areas.
- Set aside 10 percent to 15 percent of funds for Requests for Applications in specifically targeted areas of need.
- Support Program Announcements and investigator-initiated applications that target identified gaps and/or emerging opportunities.
- Enhance coordination within and among initiatives, and increase direct contact with applicants and grantees by increasing levels of extramural staff commensurate with the growth of the portfolio.
- Expand administrative supplements to encourage new collaborations that bring together basic and clinical scientists and promote additional interdisciplinary collaborations and access to central resources such as databases, tissue banks, and animal models.

Today's Research Investments Shape the Number of Researchers Tomorrow [Sidebar]

When, as in recent years, the percentage of research proposals that NCI funds (the *success rate*) averages less than 30 percent, and grants routinely are less than fully funded, young people may be discouraged from pursuing careers in cancer research and opt for professions in more stable or well-paying fields. Faced with such odds, many clinicians in particular may choose a career in private practice over clinical research. Basic cancer biology scientists may choose another career altogether.

Thus, it is not just funds for training per se that influence the number of future researchers. (See the Challenge on Training, Education, and Career Development) The success rate of the research project grant pool also makes its mark. First, many trainees depend on research project grants awarded to their mentors, rather than formal training awards, for financial support of their training. If their mentors' grants are not funded, trainees often have no immediate means to continue. Second, upon completion of their training, new investigators depend on research project grant awards for their salaries as well as for research support. Without such grants, these investigators are unable to pursue their chosen career in an academic setting. Clearly, then, reductions in the numbers of awards and the percent of recommended dollars actually awarded have profound effects on the next generation of cancer researchers.

To continue to address the many questions remaining in cancer research, NCI must assure a continuous supply of future researchers in the training pipeline. This requires more than support for the training itself. It also requires maintenance of the light at the end of the tunnel, in the form of reasonable odds for obtaining grants to sustain cancer research careers.

Centers, Networks, and Consortia

The Challenge

NCI's efforts to translate scientific knowledge into more effective cancer interventions increasingly are challenged by the conventional ways in which research is conducted. Basic, clinical, population, and behavioral scientists acquire their skills in distinctly different ways and environments, often with little opportunity to interact or work with each other. However, the rapid pace of scientific and technological discovery is creating enormous opportunities that require the close interaction and collaboration of clinical and laboratory scientists from across the research community. The challenge for NCI is to create integrated research environments that foster the complex multidisciplinary collaborations needed to address the "big picture" problems in cancer research.

These integrated research environments must functionally link basic, clinical, population, and behavioral scientists to each other and to newly developing, diverse fields of science and technology. These investigators must have easy access to many different patients and at-risk populations, tissue banks, new technologies, and state-of-the-art informatics. They must be able to work together with the same ease and flexibility in multi-institutional research settings as in the same institution.

To meet this challenge, NCI continues to create and nurture an overarching structure for research composed of NCI-designated Cancer Centers, Centers of Research Excellence, and various research networks and consortia. These centers, networks, and consortia are enhancing the traditional research enterprise in ways that promote and facilitate complex scientific interactions, provide the critical resources essential for the research, and encourage the easy exchange of information and ideas through new communications linkages. While these interactive structures are critical to progress, this challenge also requires that NCI find ways to integrate these centers and networks with each other when broader interactions will allow investigators to seek answers to major questions more efficiently and effectively.

NCI-Designated Cancer Centers

NCI-designated Cancer Centers organize and integrate multidisciplinary research across departments and schools within a single institution. Cancer Centers provide scientists access to the most advanced technologies and new research opportunities and bring the benefits of their research directly to the public in the form of patient care. They link state-of-the art research and clinical care activities within the institution and form key partnerships with industrial, community, and state health organizations outside the institution. (See http://cancer.gov/cancercenters for more information.)

For example, the disease-specific Specialized Programs of Research Excellence, designed to

move discoveries from the laboratory into patient and population research settings, had their origins in Cancer Centers. The new Special Populations Networks for Cancer Awareness Research and Training are designed to link local, community, and regional problems of cancer in underserved populations to the broad-based research capabilities of NCI-designated Cancer Centers. Centers are critical in a new NCI initiative to incorporate Minority-Serving Institutions (MSIs) into NCI's cancer research, education, training, and outreach activities. The Cancer Genetics Network sites are headquartered in Centers. Nearly all the participants in the Mouse Models of Human Cancer Consortium are in NCI-designated Cancer Centers. Centers have worked closely with industry in developing new cancer therapeutic agents and are rapidly becoming significant partners with industry for new technology development. Approximately 70 percent of cancer clinical trials are conducted in Cancer Centers.

NCI is planning to establish Regional Enhancement Cancer Centers to facilitate partnerships between smaller institutions and the large, existing NCI-designated Comprehensive Cancer Centers. These partnerships will provide patients and populations with much improved access to the newest clinical, prevention, and control trials in early detection, prevention, and therapeutic research. NCI anticipates that the centers also will play a key role in integrating and coordinating NCI-supported centers of excellence and networks into one overarching, unified research framework.

Centers of Research Excellence

Centers of Research Excellence bring together interdisciplinary and translational research teams focused on a specific disease, modality, biologic process, or scientific area. They are awarded sizeable amounts of flexible funding to enable them to rapidly address emerging scientific opportunities.

The first of these centers, the Specialized Programs of Research Excellence (SPOREs), were created in 1992 and focused on specific cancers. They serve as highly effective hubs for translational research, moving discoveries back and forth among laboratory, clinic, and population research settings. To date, SPOREs have been established in breast, prostate, lung, gastrointestinal, and ovarian cancer. (Go to spores.nci.nih.gov for further information.)

Networks and Consortia

Networks and consortia link the expertise and innovation of scientists from different disciplines and diverse research backgrounds to address important questions and issues about cancer. For example, the Cancer Genetics Network addresses the issue of inherited predisposition to cancer and is linking its goals and objectives to those of SPOREs and NCI-designated Cancer Centers. The Mouse Models of Human Cancer Consortium will work closely with SPOREs to develop mouse models that reflect various precancerous and cancerous stages of human cancer. The American College of Radiology Imaging Network, the newest of NCI's cooperative groups, is evaluating and developing a new generation of

imaging concepts and tools with device manufacturers and other technology developers. The Early Detection Research Network, which facilitates the discovery, development, and initial steps in clinical validation of molecular markers and assays that detect early signs of cancer, is already interacting with SPOREs and other interdisciplinary teams of scientists. The Special Populations Networks are involving underrepresented racial, ethnic, and minority communities in establishing research priorities and conducting research that will benefit these populations. The Pediatric Brain Tumor Consortium, a network of 10 medical centers, is evaluating promising treatments for children with brain malignancies.

Networks and consortia interact with NCI-designated Cancer Centers and Centers of Research Excellence in a seamless way to advance our understanding of cancer and to improve cancer prevention, early detection, diagnosis, and treatment.

Progress Toward Meeting The Challenge

Cancer Centers

Through its Cancer Centers Program, NCI has established the foundation for an overarching research framework that will bring diverse scientific disciplines together across institutional boundaries. **NCI-designated Cancer Centers** continue to evolve as key strategic partners of NCI. In 2001, NCI added a Center in Missouri and will fund a new planning grant for developing a Center in South Carolina. In addition, the number of Cancer Centers with the "Comprehensive" designation increased in 2001 to 38. NCI has also been working with institutions in Missouri, Georgia, New York, Louisiana, Rhode Island, Florida, West Virginia, Kentucky, Arkansas, Massachusetts, and Michigan to develop Cancer Centers.

NCI launched the **Minority Institution/Cancer Center Partnership (MICCP)** Program in Fiscal Year 2001 by funding two comprehensive partnerships, two planning grants for comprehensive partnerships, and 12 planning grants dedicated to more focused collaborative projects and programs ranging from research to training. This program reaches out to the five major minority institutions with medical schools, as well as to more than 300 smaller institutions dedicated to educating African Americans, Hispanics, Native Americans, and other groups underrepresented in biomedical research. Research-intensive NCI Cancer Centers, together with culturally sensitive MSIs, offer an entirely new set of opportunities for training more minority scientists, expanding the cancer research capability of MSIs, and focusing more research and community outreach programs of Cancer Centers on minority health disparities. In the next year, the MICCP will seek ways to integrate its efforts with NCI's Special Populations Networks for Cancer Awareness Research and Training and the Minority Biomedical Support Grant Program, sponsored by the National Institute of General Medical Sciences at the NIH.

Centers of Excellence

As NCI's **Specialized Programs of Research Excellence (SPOREs)** have become more established, SPORE investigators have begun to make significant contributions to translational research. Some recent advances reported by SPORE researchers include:

- The discovery in one of the lung SPOREs that smokers who carry certain gene types are less likely to successfully quit smoking than others. This finding helps explain why some smokers find it much more difficult to quit than others, and raises the possibility that specially tailored smoking cessation programs may help smokers with these gene types to successfully quit.

- Confirmation of a long-suspected family connection in pancreatic cancer. After tracking relatives of pancreatic cancer patients since 1994, researchers in one of the gastrointestinal SPOREs recently confirmed that relatives of pancreatic cancer patients are at higher risk for the disease. This finding not only provides important information for these relatives and their physicians, but also supplies scientists with a vital first step toward identifying the responsible genes.

- Promising results in an initial clinical trial of a "treatment vaccine" that stimulates the immune system of pancreatic cancer patients into action against their tumors. Investigators have now expanded testing of this new treatment to a larger number of patients.

As the SPORE program expands to include more centers and additional cancer sites, its investigators are expected to become a major force in translational cancer research. The SPORE program is poised to establish research centers for a number of new cancer sites every year for the next two years until there are centers devoted to every major cancer site.

The SPORE blueprint has been used to establish similar programs in other cancer research areas. Among these programs are the Transdisciplinary Tobacco Use Research Centers, *In Vivo* Cellular and Molecular Imaging Centers, the Interdisciplinary Research Teams for Molecular Target Assessment, and the soon-to-be established Centers of Excellence in Cancer Communications Research. Like the SPOREs, all of these centers support interactive, multidisciplinary research and provide research resources and flexible exploratory funds, as well as research training and career development opportunities.

The Plan – Centers, Networks, and Consortia

While NCI's goal for collaborative research applies to all NCI-designated Cancer Centers, networks, and consortia, this plan focuses primarily on the objectives and resources for the Centers and SPOREs. Many other research networks are budgeted and discussed in the

Extraordinary Opportunities and NCI Challenge sections throughout this document.

Goal

Create and sustain research infrastructures for collaboration, technology support and development, and access to resources that enable multiple scientific disciplines to address large problems in cancer that could not be solved by individual investigators.

Objectives and Milestones for Fiscal Year 2003

1. **Increase the number and broaden the geographic distribution of NCI-designated Cancer Centers and create partnerships between Minority-Serving Institutions and NCI Cancer Centers.**

- Designate one new Cancer Center.
- Award two new Cancer Center Planning Grants.
- Establish formal affiliations between Cancer Centers and Minority-Serving Institutions (MSIs) in the form of 2 comprehensive partnerships and 1 planning grant for a comprehensive partnership to enhance the research capabilities of MSIs, and improve the effectiveness of Cancer Centers in serving minority communities. (See p. x, Objective x for the training component of these partnerships.)

2. **Expand the capacity of Cancer Centers to engage in newly developing areas of research and technology and to act as platforms for translating discoveries into interventions.**

- Increase funding to all Cancer Centers to encourage scientists in Centers to develop new technologies and methodologies for entirely new approaches to answering important cancer research questions.
- Establish 10 Informatics Planning Activities in Cancer Centers to build, in partnership with NCI, critical informatics capabilities in data acquisition, analysis, integration, and coordination.
- Provide additional funding to build the clinical research and population research infrastructure of Cancer Centers. Fund databases that conform to NCI's clinical informatics infrastructure; support the development and expansion of population databases; provide more core staff to conduct innovative translational therapeutic and prevention trials; and strengthen the auditing and data safety and monitoring of human subjects research.

3. **Expand and enhance the research of Specialized Programs of Research Excellence (SPOREs).**

- Expand the SPORE program by adding one in breast cancer, two in prostate cancer, one in lung cancer, one in gynecological cancers, one in myeloma, one in genitourinary cancers, and two in leukemia.
- Support development of an Internet platform and research database to enable SPOREs to exchange research results and to foster

communications for sharing resources and developing collaborative inter-SPORE research projects.

- Provide supplements to SPOREs for planning and developing inter-SPORE research projects.

4. Implement a Strategic Supplement Program for taking advantage of high priority scientific opportunities that can be completed in a short time frame (1 to 2 years):

- In response to opportunities identified by NCI program managers of Cancer Centers, Centers of Excellence, Networks, and Consortia.
  In response to scientific advice from outside advisory groups (e.g., Progress Review Groups)

National Clinical Trials Program in Treatment and Prevention

The Challenge

Clinical trials, a crucial component of NCI's research program, are the final, definitive step in testing new approaches to cancer prevention, diagnosis, and treatment. Our National Clinical Trials Program essentially is a large and intricate laboratory without walls, through which NCI has a tangible and direct impact on the survival and quality of life of patients with cancer.

NCI's clinical trials system is complex, involves many participants, and requires collaboration at all levels – between investigators and physicians, industry and academia, academia and NCI, and NCI and industry. Adding to this complexity, our clinical trials have undergone a number of dramatic changes in recent years. Progress in cancer biology, genetics, immunology, molecular biology, and imaging technology has accelerated, creating new opportunities to improve clinical practice. As cancer researchers around the country have identified the molecular changes that cause a normal cell to become cancerous, the number of new anti-cancer agents that target these changes has rapidly grown, triggering an entirely new approach to the development of cancer drugs and a rapid growth in NCI-sponsored clinical trials for treating cancer.

At the same time, advances in informatics and electronic communications offer innovative avenues to communication and to data transfer and analysis in the clinical research setting, providing new opportunities to enhance the efficiency of clinical trials and speed their results to the care of cancer patients. NCI's cooperative groups – networks of investigators who conduct clinical trials – have begun to incorporate many of these advances into their clinical trials, but much work remains to be done.

Despite progress made to date, many barriers to clinical trials participation persist. In particular, the reimbursement that NCI provides physicians for their role in clinical trials often falls far short of their costs and is well below what the pharmaceutical industry provides. Physicians who take part in clinical trials often must hire additional nursing and data management staff to take on the tasks of ensuring that patients fully understand the risks and benefits of participation, tracking participating patients, and collecting and reporting the necessary data. A 1999 survey of oncologists by the American Society of Clinical Oncology, found that although many physicians preferred NCI-sponsored cooperative group clinical trials, inadequate reimbursement for the costs and time required for data reporting were barriers to participation.

While NCI has doubled its reimbursement over the past several years, it still lags far behind actual costs and industry standards. This problem is compounded in cancer prevention trials because many thousands of patients often are needed for an adequate evaluation of new prevention approaches, and these patients must be followed for longer periods of time.

NCI's challenge is to ensure that we are able to overcome the barriers to participation in clinical trials and that we capitalize on the latest developments in cancer research, informatics, and management for greatest efficiencies and success in addressing our most important questions in cancer prevention and treatment.

Progress Toward Meeting the Challenge

Increasing the Efficiency of Clinical Trials

In its ongoing efforts to improve the speed and efficiency with which cancer clinical trials are conducted, NCI recently centralized the common administrative, financial, and data collection activities of its clinical trials cooperative groups. Through an online Cancer Trials Support Unit (CTSU) site unveiled in 2000, cooperative group investigators can now download clinical trial protocols and other information, enroll patients in clinical trials, arrange for reimbursement of research costs, and receive alerts when new trials begin. Also beginning in 2000, investigators belonging to any one of NCI's nine cooperative groups were invited to enroll their patients in studies conducted by the other cooperative groups. In 2002, oncologists outside the cooperative groups also will be permitted to enroll their patients in these clinical trials.

Similarly, the four cooperative groups conducting studies on cancer in children merged into a single new Children's Oncology Group. The consolidation is expected to increase efficiencies, potentially doubling the number of doctors and hospitals involved in any given study and permitting trials to be completed more quickly. With cure rates for new childhood cancers now reaching 70 percent, the new cooperative group will be able to devote more of its energies to the less common childhood cancers, for which cures have been less forthcoming.

Recent Clinical Trial Results

Over the past two years, clinical trials have continued to contribute to improvements in survival and quality of life for patients with a wide variety of cancers. For example, recently completed clinical trials have determined that:

- Cervical cancer, still the second leading cause of cancer death in women around the world, can be treated more effectively by combining cisplatin chemotherapy with radiation treatment. It is estimated that this treatment can save 2,000 additional lives each year in the United States and considerably more – perhaps hundreds of thousands – worldwide.
- The combination of chemotherapy and radiation following surgery substantially prolongs the survival of patients with stomach cancer.
- For patients with metastatic kidney cancer, surgery to remove the kidney can add months

to patients' lives.

- Preoperative chemotherapy prolongs the survival of patients undergoing bladder cancer surgery.
- In the most aggressive cases of prostate cancer, radiation therapy combined with the optimal application of hormone treatments leads to longer survival.
- The use of cyclooxygenase-2 (COX-2) inhibitors has been shown to decrease the number of colon polyps and the risk of colon cancer in patients with the genetic disorder Familial Adenomatous Polyposis.

Because of findings from clinical trials, monoclonal antibodies and anti-cancer agents bound to antibodies are now prolonging patients' lives in a variety of cancers. Moreover, since trials comparing chemotherapy in young and elderly patients with lung cancer demonstrated that older patients receive similar benefits and experience no greater side effects than younger patients, more and more oncologists recognize that age should not preclude treatment or participation in clinical trials.

An Increasing Focus on Targeted Therapies

The recent improvements in cancer therapy described above generally combine advances in conventional anti-cancer treatments with surgery, chemotherapy, or radiation. But the past decade also has seen an explosion in our understanding of tumor biology and immunology, which has led to the identification of a vast array of new molecular targets at which to direct treatment and prevention interventions. The cellular pathways and interactions involved in these molecular targets are extraordinarily complex and inter-related, and they require scientists to develop new techniques and tests to identify patients whose tumors contain the relevant targets.

As a result, clinical trials of targeted agents often involve laboratory studies needed to better define the presence of targets and drug effects in the tumors of individual patients undergoing treatment. Indeed, more than half the cancer treatment trials initiated by the cooperative groups over the last two years have included correlative studies. Much the same is true of cancer prevention trials, where chemopreventive agents are targeting the molecular changes identified in pre-malignant lesions.[1] Increasingly, prevention studies must also track changes in molecular markers[2] to determine whether an intervention is successful.

Along with the discovery of more and more therapeutic targets for cancer, there has been a huge increase in the number of new anti-cancer agents in drug development. According to the Pharmaceutical Research and Manufacturers of America, more than 400 anti-cancer agents were in development in 2001, up from fewer than 100 in the late 1980s. Similarly, the number of pharmaceutical and biotechnology companies developing anti-cancer agents nearly

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[1] *Chemopreventive agents* are substances that stop the transformation of normal cells into cancer cells

[2] *Molecular markers* are cellular characteristics which, when they undergo change, provide clues that cancer may be developing.

quadrupled over the same period, rising from 45 to 170.

Despite this large increase in corporate involvement, NCI's role and the public-private partnerships it brokers continue to be essential. NCI collaborates with industry in the development of many promising investigational agents for treatment and prevention by sponsoring clinical trials for them. Because pharmaceutical companies tend to seek FDA approval or licensing of a new agent only for a single tumor type, NCI's involvement in the drug development process helps ensure that new agents are evaluated against the full range of cancers for which they may be effective and in combination with treatments such as surgery and radiation therapy. These collaborations bring new treatments and prevention strategies to patients years earlier than would otherwise occur. Figure 1 illustrates the rapid expansion of clinical trials in many different tumors, made possible by the collaboration between Novartis Pharmaceuticals and NCI-supported researchers to develop Gleevec.

Cancer Prevention Trials

As scientists discover more and more about the basic mechanisms of cancer, they also add to our knowledge about its prevention. As this knowledge accrues, experts increasingly explore the possibility of averting cancer through chemoprevention. Unlike conventional approaches to preventing cancer, which often focus on avoiding exposure to cancer- causing agents such as tobacco and excessive sunlight, chemoprevention actively intervenes against cancer with drugs or other agents that stop the transformation of normal cells into cancer cells.

One of the most widely used chemopreventive agents today is tamoxifen, a drug that interferes with the activity of estrogen and was initially introduced as a treatment for breast cancer. After physicians began to report that women who had received tamoxifen following breast cancer surgery were less likely to develop cancer in their other breast, NCI initiated the first large breast cancer prevention trial in the United States to determine whether the use of tamoxifen could prevent breast cancer in high-risk women. Initial results from that trial, announced in 1998, indicated that tamoxifen did indeed reduce the risk for breast cancer, and that its use could be especially beneficial for young women at significant risk for the disease. But because tamoxifen also carries potentially serious risks, such as blood clots and stroke, NCI continues to sponsor other clinical trials in breast cancer prevention. A major NCI-supported study is comparing tamoxifen with raloxifene, an osteoporosis prevention drug that also appears to lower the risk for breast cancer.

A number of other NCI-sponsored studies are examining the potential for the arthritis drug celecoxib (Celebrex^{TM}) to prevent colon and other cancers. For arthritis sufferers, celecoxib reduces inflammation and alleviates symptoms by inhibiting the body's production of COX-2 enzymes. Researchers suspect that celecoxib might play a valuable role in cancer prevention because precancerous tissues, such as colon polyps, also produce COX-2 enzymes, and because epidemiologic studies have shown that arthritis sufferers who regularly use celecoxib and other anti-inflammatory drugs have lower rates of colon cancer. In NCI-sponsored studies thus far, celecoxib has been found to reduce the number of colon polyps in patients

with Familial Adenomatous Polyposis, an inherited syndrome that predisposes them to colon cancer. Other NCI-funded clinical trials are investigating whether celecoxib can prevent esophageal, bladder, and skin cancers.

Figure 1 Caption

After success with a small Phase I clinical trial to test the safety of Gleevec for treating chronic myeloid leukemia, clinical investigators began testing the drug in a variety of cancers that share common molecular abnormalities. A rapid and broad expansion of clinical trials followed.

The Plan – National Clinical Trials Program in Treatment and Prevention

Goal

Ensure that NCI's clinical trials program is poised to address the most important medical and scientific questions in cancer prevention and treatment quickly and effectively through state-of-the-art clinical trials that are broadly accessible to cancer patients, populations at risk for cancer, and the physicians who care for them.

Objectives and Milestones for Fiscal Year 2003

1. **Identify and address compelling clinical questions confronting physicians and their patients struggling with cancer or at high risk of cancer.**

- Expand clinical trials planning so that critical treatment and prevention questions are addressed across the major types of conditions experiences by patients. (See Figure x.)
- Expand State of the Science meetings to cancers beyond gastrointestinal, lung, genitourinary, and leukemia to identify important research questions and define a scientific research agenda to address them.
- Provide additional research funds for scientific leadership support for researchers who chair studies in addition to caring for patients and for statisticians; together they are responsible for writing, monitoring, and analyzing NCI-sponsored, high-priority Phase III trials.
- Increase translational research funds for clinical correlative studies to uncover the mechanisms of action, response, and resistance underlying new treatments and preventive strategies and to translate basic biology from the laboratory to clinical practice.
- Support a national tissue resource system that includes normal, precancerous, and cancer tissues to facilitate rapid evaluation of new assays and relevant clinical correlations as new targets are identified.
- Fund tissue and specimen banks to store material from cancer patients

undergoing treatment and from those at risk of developing cancer to allow later studies of drug effectiveness, molecular abnormalities, and clues to tumor initiation and progression.
- Develop and make widely available through Centers of Research Excellence molecular assays required to characterize/classify tumors.

2. Enhance the ability and flexibility of the clinical trials system to respond quickly and effectively to scientific opportunities emerging from the vast expansion of molecular targets discovery, new drug discovery, and translational research.

- Create flexible collaborations between investigators to facilitate multi-institutional clinical trials, projects, and consortia
- Integrate scientific strategic planning to include cross-disciplinary input (e.g., oncology and diagnostic imaging) and project teams.
- Incorporate other relevant research questions into treatment and prevention trials, and utilize the clinical trials infrastructure more broadly.
- Incorporate behavioral, epidemiologic, outcomes, and other relevant research to effectively address cancer questions in specific tumor types and patient populations.
- Incorporate the evaluation of relevant biomarkers into clinical trials.

3. Increase the pace of development and clinical testing of promising new therapeutic and preventive agents.

- Over 2 to 3 years, substantially increase the number of promising agents entering NCI-sponsored clinical trials, triple annual patient accrual to early clinical trials of promising agents, and substantially increase the number of pivotal or proof-of-principle early clinical trials.
- Expand resources for the Rapid Access to Intervention Development (RAID) and Rapid Access to Preventive Intervention Development (RAPID) programs.
- Increase funding for early treatment and prevention agent development and for Interdisciplinary Research Teams in Interventions Directed at Molecular Targets to develop the necessary assays, tools, and approaches to assess the effects of promising new agents on their molecular targets
- Support a rapid grant review process for mechanism-based clinical trials.
- Support the infrastructure needs of the intramural clinical trials program at the NIH Clinical Center by increasing the numbers of data managers, research nurses, biostatisticians, and clinicians required to support a critical mass of clinical investigators; continue to develop the net-Trials database system to link all NCI intramural clinical investigations and to

serve as a prototype that other institutions can use; and continue the Tissue Array Research Program to identify key molecular alterations in cancers.

4. Double the rate at which Phase III trials are completed.

- Shorten the duration of patient accrual to important national trials by 50 percent, thereby substantially increasing the number of new treatments or interventions that can be definitively evaluated.
- Fund Clinical Trials Cooperative Groups, the Community Clinical Oncology Programs, and practice sites to adequately support data management and enable substantially greater physician and patient participation in clinical trials:
  - Increase the per patient reimbursement for treatment and prevention trials to adequately cover the additional nursing and data management costs required to participate in clinical trials.
  - Double the number of patients accrued to treatment and prevention trials over 1 to 2 years.
  - Provide follow-up funding to allow physicians to follow patients and report outcome data for many years and address important long-term treatment and epidemiology issues.
- Expand the Clinical Trials Support Unit to consolidate the administrative tasks associated with clinical trials and to provide a single interface for investigators enrolling patients.
- Provide extensive information about prevention and treatment options and clinical trials to enable patients and physicians to make informed medical choices.
- Facilitate clinical trials participation by developing uniform electronic case report forms and data reporting systems.

5. Reduce outcome disparities in special populations by increasing access to state-of-the-art clinical trials in cancer prevention and treatment.

- Expand Clinical Trials Outreach Programs to increase participation by underrepresented populations; establish clinical trials units at historically black and other minority medical institutions; strengthen clinical trials units at minority-based community oncology sites.
- Increase clinical trials participation by minority physicians and health professionals by implementing: (1) an NCI fellowship training program in clinical trials for minority physicians and (2) forums for minority scientists' input into developing clinical trials that address issues of special importance for minority and special populations.

Studying Emerging Trends in Cancer

The Challenge

Over the past few decades, NCI has worked with other agencies to create a national cancer surveillance system for tracking cancer trends. At the heart of this system is the monitoring of *cancer incidence*– the number of people per 100,000 who develop cancer in a given year - and *cancer mortality*– the number of people per 100,000 who die from cancer each year. The system is also able to track cancers that may be declining or on the rise. Because of cancer surveillance, for example, we know that since 1990, the rates of both new cancers and deaths have fallen for all cancers combined and for most of the top 10 cancers, reversing a decades-long trend of rising rates in the United States. However, we are striving to build a surveillance system that not only tracks cancer statistics, but also helps us form hypotheses for cancer research, make critical scientific and public health decisions about this disease, develop prevention and control measures, and assess whether interventions are making a difference. Recent rapid advances in computerized information technology, increasing diversity in the U.S. population, and changes in health care delivery present new challenges to building such a surveillance system. For NCI to continue its pivotal role in effective and comprehensive national surveillance in a changing cultural, social, and technological milieu, we must respond on at least three fronts.

First, we must **improve surveillance activities on several levels**. We must create up-to-date statistical and analytical measures and improve the ways we apply the data. NCI's Surveillance, Epidemiology, and End Results (SEER) program must cover a broader spectrum of the population and compare information on why people get cancer and how it is treated with outcomes such as quality of life, and mortality. We must improve the measures we use to track cancer risk, screening practices, treatment, quality of life, quality of care, and morbidity. Improved surveillance programs must also integrate measures related to physicians, health systems, cancer communities, and policy into local and regional databases. We need to apply these comprehensive improvements to help the cancer community identify areas to target for research and for health policy and planning.

Second, we must **develop research tools that will allow us to track cancer trends more completely and more precisely**. We must improve the way we make cancer surveillance data available electronically to ensure the privacy and confidentiality of individuals. New trend modeling techniques are needed to help us explain the trends across the cancer continuum. Health-related geographic information systems are needed to examine regional cancer data on individuals in relation to potential environmental exposures. Cancer maps must be refined to allow easier application of statistical analyses that measure cancer patterns and identify cancer clusters.

And third, we must **enhance dissemination of surveillance data to scientists, the public, and policy makers.** Cancer surveillance data will have its greatest impact on reducing the

cancer burden only if it is provided in a timely manner and in a readily usable format to those who need it.

Progress Toward Meeting the Challenge

Working with new partners, NCI has improved and expanded its Surveillance, Epidemiology, and End Results (SEER) program, created new surveillance tools, and put in place mechanisms to improve dissemination of surveillance data.

Activities To Improve Surveillance

NCI has worked with its partners to build a broader surveillance program that can aid cancer planning, especially at the state and local level.

- We have **expanded and improved the efficiency and utility of SEER** (http://www.seer.cancer.gov) on several fronts. Four new SEER registries have expanded coverage of rural Whites and Blacks, non-Mexican Hispanics, American Indians, and states with high poverty and/or cancer death rates. Collaborative ventures with the Centers for Disease Control and Prevention (CDC) and other registries coordinate collection and use of national and state cancer data. Simpler, standardized rules for data collection create consistency among U.S. population-based cancer registries.

- We have **expanded data on risk, health behaviors, and screening at the state and local level**. We have collected nationwide tobacco tracking data (see Tobacco Extraordinary Opportunity, page x) and conducted an in-depth evaluation, through the Cancer Research Network, of tobacco control delivered within medical practices across the United States.

  We have enhanced the dietary data collected in the National Nutritional and Health Examination Surveys by the National Center for Health Statistics in order to improve tracking of progress made towards achieving the Healthy People 2010 nutrition objectives relevant to cancer control.

  The 2000 National Health Interview Survey Cancer Control Topical Module – a survey of cancer risk, health behaviors, and screening conducted in collaboration with the National Center for Health Statistics (www-dccps.ims.nci.nih.gov/ARP/RiskFactor/nhis_ccs) – was released in the fall of 2001. This survey provides data for tracking progress in cancer control health practices, genetic testing issues, and other cancer-related health objectives.

  We have used survey data to assess how community physicians use new knowledge about cancer risk, screening, and treatment (www-dccps.ims.nci.nih.gov/ARP/physician). A completed national Survey of Colorectal Cancer Screening Practices in Health Care among 2,212 physicians helps identify potential targets for improving compliance with

recommended screening. A national Physician Survey on Cancer Susceptibility Testing examined comfort with and use of genetic susceptibility testing among 1,250 physicians.

- NCI **has expanded research on the adoption of new advances in cancer treatment and how their use affects quality of life and patient-centered outcomes.** We have evaluated the diffusion into the cancer community of new cancer treatment advances; especially those highlighted by successful clinical trials, the NIH Consensus Development Conference reports, and NCI clinical alerts. For example, patterns of care studies are drawing from a rich abundance of existing SEER registry data to quantify adoption of recommended treatments for breast and colon cancer. These ongoing studies and the Cancer Care Outcomes Research and Surveillance Consortium (CANCORS) are expected to provide the basis to evaluate cancer treatments, quality of care, and their effect on quality of life and other patient-centered outcomes. We have supported projects focused on the economics of cancer and on using claims data for evaluation of cancer health services. We also have expanded our research among cancer survivors, examining lifestyle and quality of life in relation to cancer treatment and survival. For example a seminal workshop co-sponsored by public and private cancer organizations examined the role of physical activity across the cancer continuum. An NCI-funded study – Health, Eating, Activity, and Lifestyle and Breast Cancer Prognosis – examined these factors among ethnically diverse community-based breast cancer survivors.

- We have been **linking data on risk, screening, and treatment to outcomes**. An NCI/CDC/California State Department of Public Health venture, the California Health Interview Survey (www-dccps.ims.nci.nih.gov/ARP/RiskFactor/chis.html), provides a rich assessment of social, cultural, health system, and policy measures critical to local cancer control policy and planning in the diverse population of California. We also have linked mammographic screening data in diverse communities to cancer outcomes in the NCI-supported Breast Cancer Surveillance Consortium (www-dccps.ims.nci.nih.gov/BCSC) in order to provide national measures of mammography performance.

Development, Delivery, and Improvement of Research Tools

To better track emerging trends in cancer and apply the data to reduce the national cancer burden, we have been providing new tools for exploring patterns and generating hypotheses for etiologic research, which examines the causes behind cancer cases.

- The **Geographic Information Systems (GIS) for cancer control** is an analytical tool that complements the *Atlas of Cancer Mortality in the United States* (http://www.nci.nih.gov/atlas). While the **Atlas of Cancer Mortality in the United States** shows geographic patterns of cancer death rates and makes it easy to uncover cancer patterns, **Geographic Information Systems (GIS**) provide tools for exploring patterns and generating hypotheses for etiologic research. Two major improvements have

been made to this specialized GIS. The first, the Geographic-Based Research in Cancer Control and Epidemiology (http://www-dccps.ims.nci.nih.gov/SRAB/gis), supports use of the *Cancer Atlas*, GIS and other innovative methodologic research in geospatial statistical analysis. Collaboration with the National Science Foundation Digital Government Initiative supports method development for better visualization of spatial data. This effort will help both scientists and non-scientists to comprehend these data.

- **Cancer Profiles**, a system for identifying geographic areas in greatest need of cancer control activities, is being constructed in collaboration with CDC and other partners. The Web-based interactive design will allow users to identify regions that match user-specified statistical and trend comparison criteria. The system will provide high quality data on ecologic measures, such as demographic, socioeconomic, and other such measures that relate the effects of physical and social environments to cancer trends. Ecologic measures are valuable for planning cancer control strategies. This system will use advanced statistical methods to pinpoint the cancers that contribute most to recent state and national trends.

- **Analytic tool kits** developed by NCI, such as SEER Stat and associated statistical modules, facilitate the use of SEER and other cancer surveillance databases. Enhancements include ease of use, innovative new statistical measures, and improvements to existing measures and statistical modules. Development of database management systems for SEER is making registry operations more efficient and promoting uniform standards and consistency of implementation.

Improving Dissemination and Diffusion in Cancer Surveillance

To communicate and promote the use of important information about cancer trends, NCI has been improving dissemination and diffusion of data resources and methods. We have added mechanisms that provide important information about cancer trends not only to cancer centers, universities, and health departments, but also to cancer advocates and the public.

- Special **resources have been mounted on the Web to make complex national data systems such as SEER much easier to use**. These resources include the Current Population Survey Tobacco Use Supplements, the improved SEER-Medicare Linked Database, the International Dietary Assessment Calibration/Validation Research Register, SEER*Stat, SEER*Prep, SATSCAN, CANSURV, COMPREV, the CanQues, and SEER training Web- hosting services.

- NCI is **examining the potential use of workshops to teach proficient use of methodological and statistical applications**. Examples include workshops on using analytic methods for complex medical claims data in the SEER-Medicare Linked Database and exploration of innovations in statistical methods for surveillance.

- We are **collaborating with public and private partners to organize and streamline data collection, statistical methods, and reporting processes**. For example, starting with the Web-based statistical module CanQues, a major international publishing company is helping to make a "core engine" that can be used online to retrieve cancer statistics. Collaborations with the Breast Cancer Surveillance Consortium and the Breast Imaging Reporting and Data System Committee of the American College of Radiology are releasing the research potential of national mammography screening data by streamlining and standardizing data collection instruments and software systems.

- NCI will publish the *Cancer Progress Report*, in hard copy and on the Web, to detail progress in our Nation's fight against cancer.

NCI scientists have also been **studying the impact of interventions on cancer trends at state, local, and national levels** through support of the Cancer Intervention and Surveillance Modeling Network (CISNET) (http://www-dccps.ims.nci.nih.gov/SRAB/cisnet.html). CISNET explores the causes of cancer incidence and mortality trends, analyzes whether recommended interventions are working, predicts the impact of new interventions, and studies optimal control strategies. As requested through state health departments and American Cancer Society (ACS) divisions, and in collaboration with CDC and ACS National, we are building relationships between cancer control planners and CISNET to model the impact of disseminating effective interventions on cancer trends.

The Plan – Studying Emerging Trends in Cancer

Goal

Expand cancer surveillance data systems, methods, communications, and training to improve capacity for monitoring progress in cancer control and to explain potential causes of cancer nationally and among diverse populations.

Objectives and Milestones for Fiscal Year 2003

1. **Improve cancer registry data by expanding Surveillance, Epidemiology, and End Results (SEER) coverage, improving the quality of all population-based cancer registries, and enhancing SEER as a research resource.**

- Refine and harmonize federal cancer registry programs (i.e. four new expansion registries added to SEER to improve coverage of key populations) to meet SEER standards for data quality, and use the data for reporting and for cancer control activities.
- Identify registry operations that will help meet SEER standards by implementing and improving quality assurance procedures and use of data quality profiles. Improve coordinated federal cancer registry programs through development of enhanced information technology systems for registry operations in SEER programs.

- Support innovative statistical survey research methodology and complex regression models for combining data from diverse sources to meet the needs of the evolving national cancer surveillance data.

2. Expand systems and methods to enhance the quality of cancer control data on risk, health and behaviors, and screening practices linked to high quality data on cancer outcomes.

- Continue the Current Population Survey (CPS) Tobacco Use Supplements, with the 2003 survey focusing on key tobacco cessation issues, and extend support for analytic tools, resources, and investigator-initiated research to use a decade of CPS Tobacco Use Supplements for evaluating local, regional, and national progress in tobacco control.
- Enhance national and regional data systems to improve measurement of key issues for cancer trends and data on socioeconomic and other demographic measures. Initiate data tracking systems for cancer control and treatment drugs and for over-the-counter prescription drugs and complementary and alternative therapies. Support development of a restricted access research data center required for linked databases containing potentially identifiable information.
- Continue supporting surveillance screening initiatives:
  - In collaboration with the Agency for Healthcare Research and Quality, develop a surveillance and behavioral colorectal cancer screening initiative to improve compliance with screening and monitor performance in primary care practices.
  - Explore data systems to monitor the use and side effects of spiral computed tomography for lung cancer and the role of Pap smears versus Human Papilloma Virus testing for cervical cancer screening.
- Expand the Cancer Research Network as a population laboratory for evaluating progress in cancer control and care within integrated health care delivery systems.
- Collaborate with private and public partners to facilitate transition phase of obtaining cancer stage and care data in 2003 that is not currently part of routine cancer registration.
- Update linked databases for tracking cancer care, such as the linked SEER-Medicare database, and develop new linked databases related to cancer control and treatment at the population level for people under age 65.
- Use statistical and methodological research to improve the accuracy and reliability of cancer- relevant measures - including self-report and biological diet measures, physical activity, and social and psychological behavioral determinants – for use in surveillance and epidemiologic research.
- Develop statistical and graphical methods, software applications, and other technologies relevant to geospatial and mapping research.

3. Expand systems and methods to enhance capacity for exploring causes of cancer, generating new hypotheses on risk, and identifying new opportunities for cancer control interventions.

- Encourage use of NCI *Atlas of Cancer Mortality in the United States, 1950-1994*,

and other population-based data systems (e.g. Long Island Breast Cancer Study), as a source of study from high-risk areas.

- Provide critical tools for cancer control, especially at the community level, by developing a Web-based Internet lecture series on use of Geographical Information Systems (GIS) and other data sources for cancer control research; working with the National Science Foundation on use of geographical data; and developing analytic and graphic software for visualizing disease patterns and advancing use of disease-exposure GIS applications.
- Support workshops and pilot study on enhancing surveillance systems for research in gene-environment interactions and identifying the potential for cancer control interventions at the population level.

4. Improve dissemination of information on cancer trends and progress in cancer control and care to researchers, public health professionals, the public, policymakers, advocates, and legislators. Enhance training opportunities in surveillance, health services, and applied research.

- Continue public and private collaboration to expand local and national surveillance data dissemination for research and health policy planning, applying information technology to enhance visual quality, user interaction, and clarity for a diverse audience.
- Continue the NCI *Cancer Progress Report* as a vehicle for disseminating summaries of cancer progress, including new measures and a 2003 feature on dissemination of cancer treatment advances.
- Support a Surveillance Evidence Review on cancers with adverse trends to evaluate research on epidemiologic, surveillance, and treatment factors influencing trends, and collaboratively apply the data to develop focused health policy and plans to improve trends.
- Fund existing surveillance and applied research networks and consortia to conduct intensive training programs, provide sabbatical opportunities for research professionals, and initiate and develop academic curricula on surveillance, health services, and applied research.

Quality of Cancer Care

The Challenge

About nine million Americans living today have had a diagnosis of cancer, and another 1.3 million will be diagnosed in 2001. Of these, a large percentage are undergoing active treatment for their disease, and all require life-long quality care to detect and treat recurrences, new cancers, and treatment side effects, as well as to meet their supportive care needs. In 2001, direct medical care costs attributable to cancer will exceed $50 billion. The toll in human pain, suffering, and fear cannot be captured in dollars, but will be keenly felt by the millions of people with cancer, their families, and caregivers.

The quality of cancer care is a major national concern. Evidence suggests that some patients with cancer do not receive the newest known effective treatments. Moreover, in some cases, there remains substantial disagreement or uncertainty about what constitutes optimal care, especially from the patient's perspective. This was underscored by reports from the Institute of Medicine's National Cancer Policy Board – *Ensuring the Quality of Cancer Care* and *Improving Palliative Care for Cancer* – and by the President's Cancer Panel meetings held across the country to explore why not all Americans get the best available cancer care. These analyses and proposals for change point to an emerging consensus about the critical elements of a research agenda to improve the quality of cancer care.

To meet our challenge of improving the quality of cancer care, we must:

- Define **a core set of cancer outcome measures** to enhance our ability to compare interventions across studies and over time. Outcome measures are specific "end result" measures that tell us something about how well the interventions worked. Chosen measures must be patient-centered, acceptable to providers and payers, span the continuum of care from prevention to treatment and post- treatment care, including palliative care, and meet the highest technical standards of validity, reliability, and sensitivity to change.
- Define **a core set of process measures** to identify those interventions that have been convincingly shown to improve cancer care outcomes. Process measures are focused on how care is delivered in comparison with accepted standards.
- Build a **stronger data and methods "infrastructure" for conducting quality of care analyses**, including studies to determine which interventions improve patient-valued outcomes, identify geographic or racial/ethnic variations in receipt of quality care, and monitor quality over time, both at the individual and population levels.
- Ensure that **therapies shown to be effective in clinical trials go to community practice**.
- Enhance the **quality of cancer communications** – for example, between patients and providers, between news media and patients, and between a patient's family and third-party payers – by gaining a better understanding of the information needs of patients, families, and other decision makers involved in the choice of cancer interventions.

Progress Toward Meeting the Challenge

The challenge of improving the quality of cancer care is enormous and multifaceted. The following are examples of some specific research activities underway related to key elements of NCI's quality of care research plan.

Developing Core Measurements for Assessing Quality of Cancer Care

Core Outcome Measures
Identifying clinical and patient-centered endpoint measures that are valid, reliable, sensitive, and feasible for use in quality of care studies is critical if these studies are to appropriately inform decision makers. In response, NCI has convened 35 internationally recognized experts in measurement, oncology, and the social sciences to assess the strengths and limitations of alternative approaches to measuring health-related quality of life, economic burden, and satisfaction with care for the major cancer sites and for every phase of cancer care. This group, the Cancer Outcomes Measurement Working Group, will contribute to NCI's ability to identify core endpoint measures for use in a variety of quality of care analyses, including controlled clinical trials and observational studies.

A set of papers reviewing and analyzing the published literature in cancer outcomes research over the past decade will be published as a monograph of the *Journal of the National Cancer Institute* in early 2002. This monograph will critically appraise the current and potential use of cancer outcomes measures across a broad array of applications – from national level surveillance, to the evaluation of prevention and treatment interventions in trials or observational studies, to monitoring the progress of individual patients undergoing cancer treatment.

Core Process Measures
For some elements of cancer care, there is such strong evidence linking performance to better outcomes that providing such care is presumed to enhance quality. By the same token, failure to provide this care is an indicator of inadequate quality. Therefore, a body of such core process measures of cancer care quality would constitute important standards for ongoing and future research to monitor the performance of providers and health systems. The availability of these measures would sharpen the focus of analyses of population disparities in the availability and delivery of quality care. And, as the National Cancer Policy Board has recommended, an ideal national cancer data system would include such a core set of process measures so that the quality of cancer care could be efficiently and effectively monitored within and across geographic areas, as well as over time.

To move this effort forward, NCI is working closely with the **National Quality Forum** (NQF), created recently to foster voluntary consensus standards on the quality of health care, focusing on treatment, survivorship, and palliative care. NCI has actively collaborated with a number of Federal agencies and private- sector organizations to assist the NQF in shaping the

objectives, agenda, framework, and timeline, as well as to provide financial and technical assistance. Organizations and agencies joining with NCI in this effort include the American Society of Clinical Oncology, the American College of Surgeons, the American Cancer Society, the National Comprehensive Cancer Network, the National Committee for Quality Assurance, the Joint Commission on Accreditation of Healthcare Organizations, large payer and provider organizations, and all the Federal agency members of the Quality of Cancer Care Committee.

Strengthening the Science Base for Quality Cancer Care Assessment

NCI's **Surveillance, Epidemiology, and End Results (SEER) program**, a well known and highly respected surveillance system, has provided a wealth of information to the private and public research enterprise on the cancer burden, as well as data resources for assessing the impact of research advances on cancer outcomes. **SEER Pattern of Care Studies** are ongoing investigations to monitor the diffusion of cutting-edge interventions into community practice, with special attention to population disparities in the receipt of cancer care. Benchmark studies from 1987 to 1995 on patterns of care for patients with breast and colorectal cancer will be published in 2001.

The Prostate Cancer Outcome Studies (PCOS), initiated in 1994, have extended our ability to understand treatment patterns by collecting information directly from patients and their physicians, as well as data from medical records, for more than 3,500 men diagnosed with prostate cancer and followed for up to 5 years. For men with prostate cancer, the treatment choice is frequently difficult, often involving a joint consideration of the patient's age, the presence of other medical conditions, and an estimate of how fast the tumor is growing. Current treatment options include watchful waiting, surgery, radiation therapy, or hormone therapy, all of which hold some risk and benefit to the patient.

Findings from PCOS will contribute to more informed treatment decisions for men diagnosed with prostate cancer. These results include detailed descriptions of treatment effectiveness, side effects, and the resulting impact on health-related quality of life. For example, results from a PCOS study looking at health outcomes after radical prostatectomy or radiotherapy for clinically localized prostate cancer show that rates of impotence are high among men receiving radical prostatectomy (79 percent) and radiation (62 percent). Among the men ages 55 to 59 years, the prostatectomy patients were more bothered by loss of sexual function than were the radiotherapy patients. Also, men in the radical prostatectomy group recovered some urinary and sexual function during the second year after treatment, while men in the radiotherapy group remained the same or slightly worse.

PCOS results **also are providing information on racial and ethnic differences in advanced- stage prostate cancer**. One recently published report shows that African American and Hispanic men are more likely to be diagnosed with advanced- stage prostate cancer than are White men. For Hispanics, but not for African Americans, much of this difference is explained by differences in demographic, socioeconomic, clinical, and health

insurance patterns. These results suggest that more targeted research is needed to identify the specific life-style, attitudinal, and health system factors, as well as biological susceptibility factors, that may explain these higher rates of advanced- stage prostate cancer in these ethnic groups.

The approach of using large cohorts of newly diagnosed cancer patients to study treatment patterns and the linkage between the processes of care and outcomes has been extended to the study of colorectal and lung cancers. At research institutions across the country, NCI is providing support for research teams to conduct these studies under the sponsorship of the **Cancer Care Outcomes Research and Surveillance (CanCORS) Consortium.** CanCORS will support the development and application of an expanded set of core process and outcome measures and will examine methodological issues in outcomes research conducted in community settings.

Studies linking **SEER and Medicare data** are also extremely useful to the research community and other stakeholders assessing the quality of cancer care. Recently published SEER-Medicare studies include examinations of the use of palliative chemotherapy, surveillance procedures to monitor cancer recurrence, and investigations of cancer clinical outcomes as a function of hospital volume.

A study looking at age and adjuvant chemotherapy use following surgery for Stage III colon cancer reports that more than 70 percent of Stage III colon cancer patients ages 65–74 initiated postoperative chemotherapy during the period 1991 - 1996. However, rates of use declined markedly for older patients, even after adjusting for measures of comorbidity. Also, African American patients were found to be less likely to receive chemotherapy than Whites, even among patients with no major comorbidities. Further investigation is necessary to determine whether patient preferences, physician attitudes, or other factors in the health care system explain the care patterns.

In an effort to develop analogous information and data on patients under 65 years of age, NCI has been working with managed care systems to promote collaborative cancer research. Through the **Cancer Research Network (CRN) initiative**, a consortium of researchers affiliated with 10 major not-for-profit HMOs is conducting studies of late- stage breast and invasive cervical cancer cases to identify patient, provider, and system factors that affect advanced disease. Through funding from the Agency of Healthcare Research and Quality, the CRN is developing a complementary pharmacological database. Along with the development and validation of methods to increase the utility of HMO automated data in cancer- related health services research, the CRN will facilitate the rapid conduct of patterns-of-care and quality improvement studies as well as studies of pre-existing disease conditions and drugs as risk factors for uncommon cancers.

Enhancing Quality of Care Research within the NCI Clinical Trials Program

The NCI clinical trials program provides an ideal venue to assess quality of care by

incorporating valid, reliable, quality- of- life endpoints into clinical study design. Staff of NCI's divisions with an interest in cancer treatment, diagnosis, prevention, survivorship, end-of-life care, and outcomes research are working with clinical trials investigators around the country to assist them in decisions about the appropriate inclusion of quality-of-life endpoints in NCI-sponsored trials.

Improving the Quality of Cancer Care by Strengthening Cancer Communications

Ultimately, improved cancer care depends on our ability to translate messages about prevention, treatment, patient care, survivorship, and end-of-life issues to the research community, providers, patients, and payers. As part of NCI's investment in Cancer Communications as an Extraordinary Opportunity (see pages xx), several efforts already underway focus directly on the quality of cancer care. For example, one study is evaluating information and communication needs of adult cancer survivors prior to and following adjuvant therapy, and another is investigating the skills of individuals at high risk for particular cancers and their ability to understand probability data associated with their increased risk.

Ensuring the Best Available Scientific Evidence on Quality Measures and Assessment To Inform Federal Decision Making on Cancer Care

In 1999, the Department of Health and Human Services created the Quality of Cancer Care Committee (QCCC), a trans-agency task force with representatives from Federal agencies involved in cancer care delivery (e.g., Department of Veterans Affairs), coverage (e.g., Centers for Medicare and Medicaid Services, formerly the Health Care Financing Administration), regulation (Food and Drug Administration), and research (Agency for Healthcare Research and Quality). The QCCC, chaired by NCI, was created on the principle that Federal-level decisions about cancer care should be consistent with the best scientific evidence available on quality outcomes. Through this forum, NCI is drawing on its own research base and expertise to contribute to a number of projects. By July 2001, the QCCC had inventoried current Federal agency projects bearing on the quality of cancer care, identified agency information needs, and launched four inter-agency collaborations for which NCI is supporting efforts to improve translation of evidence into practice. NCI is working directly with:

- **The Department of Veterans Affairs,** on a project to improve detection and treatment in colorectal cancer care. NCI is funding and will serve in a liaison advisory capacity for a Quality Enhancement Research Initiative Center to promote use of evidence to foster better patient outcomes and promote ongoing system wide improvements in detection and treatment of colorectal cancer.

- **The Centers for Medicare and Medicaid Services,** on a project to improve the quality of cancer care by increasing colorectal cancer screening rates within the Medicare

beneficiary population and their primary care physicians in North and South Carolina.

- **The Health Resources and Services Administration (HRSA) and the Centers for Disease Control and Prevention,** on a project to improve cancer screening, referral, and follow- up in Federally supported primary care health clinics. One objective of this project is to reduce health disparities for the underserved population cared for by HRSA-supported community health centers throughout the. United States.

- **The Food and Drug Administration,** in an effort to determine the benefit of selected endpoints, including clinically oriented and patient-reported outcomes, to help judge drug efficacy and health marketing claims. The aim is to understand the value added – in terms of information important to patients and other decision makers – that can be gained from a given measure of health-related quality of life in addition to, or instead of, symptom-based indicators of patient status and improved survival.

The Plan – Quality of Cancer Care

Goal

Enhance the state of the science for defining, measuring, monitoring, and improving the quality of cancer care, and inform both public- and private- sector decision making on cancer care delivery, coverage, regulation, and standards setting.

Objective and Milestones for Fiscal Year 2003

1. **Develop core process and outcome measures for assessing the quality of cancer care.**

- Support research to improve the theory and practice of patient-centered outcomes measurement in cancer. These will include development and testing of new instruments, item banking, and computer adaptive testing to improve the efficiency and accuracy of data collection as well as statistical studies to facilitate the "cross-walking" of scores between competing instruments.
- Continue to participate in and provide supplemental funding for the public-private committee process established by the National Quality Forum in order to identify core process measures of cancer care quality.

2. **Strengthen the methodological and empirical foundations of quality of cancer care assessment.**

- Sustain support for Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) studies of the impact of targeted interventions on patient-centered outcomes, dissemination of state-of-the-science therapies and palliative care into community practice, the influence of modifiable risk factors, and disparities in the delivery of quality cancer care, focusing on cohorts with large numbers of colorectal and lung cancer patients.

- Sustain support for Cancer Research Network population laboratories for cancer control research, with additional emphasis on studies of the quality of cancer care in community settings.
- Sustain support for Surveillance Epidemiology and End Result program (SEER) pattern of care studies to produce regular and timely information on levels, trends, variations, and dissemination of treatments of proven efficacy and effectiveness, including cutting-edge initial therapies, follow-up care, and palliative interventions. Integrate results from these studies with Cancer Intervention Surveillance Modeling Network (CISNET) models to predict effects of treatment dissemination on population trends in cancer survival and mortality.
- Increase support for analyses of the linked SEER-Medicare database to investigate the diffusion and outcomes of selected cancer interventions, with special emphasis on whether differential application of interventions contributes to cancer outcome disparities among people age 65 and older.
- Support the creation of databases that link tumor registry information with private payer administrative data to expand capacity to investigate whether cancer interventions are reaching and improving the health of individuals under age 65.
- Continue support for innovative research on economic and health care delivery system determinants of quality of cancer prevention, screening, and treatment services at the community level.
- Sponsor new studies to strengthen the methodological foundations of outcomes research and quality- of- care assessment.

3. Enhance quality of care research within the NCI clinical trials program.

- Sponsor a symposium and follow-up workshop to bring together leading researchers, patient advocates, and the relevant Federal agencies to assess the current state of the art, identify key research questions, and develop a decision strategy for encouraging comprehensive assessment of patient outcomes for clinical trials.
- Using knowledge gleaned from a workshop on the determinants of diffusion of medical innovations, expand support for studies of diffusion patterns and the overall diffusion rates of important clinical trial findings into community practice.

4. Improve the quality of cancer care by strengthening the quality of cancer communications.

- Gather and analyze nationally representative data to assess the current status of cancer communications and their use in cancer care decision making.
- Within the Centers of Excellence in Cancer Communications Research, support projects to improve patients' understanding of the risks, benefits, and costs of curative therapies and palliative interventions.
- Create new communications products and tools to improve the accuracy,

clarity and timeliness of cancer care decision making.

- To accelerate the adoption of important patient interventions, convene an interdisciplinary group of scholars, organization gatekeepers, and funders to identify research strategies and opportunities for collaboration.

5. Ensure that the best available scientific evidence about quality measures and assessment informs Federal decision making on cancer care. Share new knowledge with public and private partners on ways to translate quality-of-care research into better medical practice. Collaborate with these partners to identify core measures of cancer care quality.

- Continue to support interagency demonstration projects organized through the Quality of Cancer Care Committee, a forum for coordinating Federal activities to improve the quality of cancer care. These projects include NCI's ongoing collaborations with the Department of Veterans Affairs, the Centers for Medicare and Medicaid Services, the Health Resources and Services Administration, and the Food and Drug Administration.
- Capitalize on the collective clinical and policy expertise of the QCCC to provide technical assistance and advice to public agencies and private organizations upon request.
- Work closely with QCCC member agencies in identifying the appropriate Federal role in, and contributions to, the public-private consensus process convened by the National Quality Forum to establish core measures of cancer care quality.

Reducing Cancer-Related Health Disparities

The Challenge

Disease results from a combination of risks related to genes, individual behaviors, and social and environmental circumstances. The interaction among these various factors ultimately determines who is born healthy, who grows up healthy, who sustains health throughout his or her life span, who survives disease, and who maintains a good quality of life after diagnosis and treatment. NCI's long-term investment in biological research and our more recent investments in behavioral research have helped us make enormous strides in understanding how biological and behavioral factors determine risks for developing or dying from cancer and how interventions can modify these risks. Much less is known, however, about the effect that factors such as social position, economic status, cultural beliefs and practices, and environmental exposures have on cancer risk.

The unequal burden of disease in our society is a challenge to science and a moral and ethical dilemma for our Nation. To reduce and eventually eliminate cancer-related health disparities in our society, we must develop an understanding of the interface where biological, behavioral, social, economic, cultural, and environmental factors meet. We must separate myth from reality to determine what does and does not contribute to these disparities and use that insight to develop new interventions. And we must make new research investments to explain:

- The relative importance of social, cultural, and environmental determinants of cancer
- How social, cultural, and environmental factors interact with biological and behavioral determinants
- By what mechanisms social, cultural, and environmental determinants may increase cancer incidence and mortality and contribute to cancer-related health disparities

Progress Toward Meeting the Challenge

As a result of external and internal reviews of cancer health disparity issues and research programs, NCI is working in several high-priority areas to close the gap between what we know about cancer care and how and to whom it is provided.

- NCI-sponsored **Special Populations Networks for Cancer Awareness Research and Training (SPNs)** were established at 18 research institutions in 2000. The SPNs will build relationships with community-based programs to foster cancer awareness activities, increase minority enrollment in clinical trials, and develop minority junior biomedical researchers through cancer control, prevention, research, and training programs in minority and underserved communities.

  In the first year of this program, each SPN has (1) developed new culturally and

educationally appropriate cancer awareness campaigns focused on African American, Asian American, Pacific Islander, Latin American, Native American, and low-income Appalachian white populations and (2) built collaborative, community-based infrastructures for cancer control research.

Also, fourteen of the SPNs have worked to increase the competitiveness of junior and minority investigator-initiated research applications submitted for peer review by participating in a first round of developmental research grants program sponsored by NCI.

- Two new series of **cancer patient education materials for low-literacy populations** focus on information in two areas important to these groups, pain management and clinical trials. The pain management information was adapted from materials developed by the Johns Hopkins University Comprehensive Cancer Center. The clinical trials series was created specifically for African American and Native American groups.

- NCI collaborated with the Howard University Cancer Center and Meharry Medical College to increase **access to and involvement in clinical trials by underrepresented populations, minority researchers, and patients and physicians** who have not previously participated in clinical trials research. NCI provided support for the development of culturally appropriate patient education materials and for clinical trials data management infrastructure.

- NCI is focusing increased attention on **how best to translate research into improved outcomes for all populations**. NCI leadership helped organize the Department of Health and Human Services (DHHS) task force on the dissemination of health promotion and disease prevention interventions. The Institute has contributed to the training of state health department staff and volunteers from 17 divisions of the American Cancer Society (ACS) in best practices for using data to improve cancer control planning, collaboration with ACS and the Centers for Disease Control and Prevention (CDC). The Institute has worked with the CDC to develop a targeted dissemination plan for evidence-based cancer control interventions to be included in the *Guide to Community Preventive Services*.

  NCI has worked with the Agency for Healthcare Research and Quality and CDC to promote the adoption of best practices for clinical and public health approaches to tobacco control. The Institute is working with the ACS and NCI-funded researchers to disseminate a dietary intervention through faith-based organizations, tested with the NCI 5-A-Day research grant support, and found to be effective in two studies conducted among six Black churches in North Carolina and Georgia. Working with ACS regional and Black church volunteers, NCI is supporting dissemination research of a unified *Body and Soul* program in nine matched pairs of Black churches in three regions, and ACS will provide sustained support for the intervention.

- NCI is providing **training for new scientists focused on health disparities** through the

Cancer Prevention Fellowship Program and the Special Population Networks for Cancer Awareness Research and Training (SPNs). In the Washington, D.C., area, fellows have research and mentor opportunities through the NCI-funded Latin American Cancer Research Coalition SPN. This arrangement provides participants with field experience at Georgetown University and Washington Hospital Center. Similarly, a Cancer Prevention Fellow is working closely with investigators at the Johns Hopkins Oncology Center in new prevention and control programs targeted to African American men in Baltimore City and Prince George's County.

Highlights of Recent Research on Cancer-Related Health Disparities

Treatment Disparities for Lung Cancer. An NCI-funded study found that the lower survival rate among Black patients with early-stage, non-small-cell lung cancer, as compared with White patients, is largely explained by the lower rate of surgical treatment among Blacks. This study of 10,984 Stage I or II non-small-cell lung cancer patients 65 years of age or older (of whom 860 were Black and 10,124 were non-Hispanic White) showed that:

- The rate of surgery was 12.7 percentage points lower for Black patients than for White patients (64.0 percent versus 76.7 percent).
- The 5-year survival rate was also lower for Blacks (26.4 percent versus 34.1 percent).
- For patients who had surgery, survival was similar for the two racial groups.
- For patients who did not have surgery, survival was also similar.

These analyses suggest that increasing the rate of surgical treatment for Black patients would appear to be a promising way to improve survival in this group.

Cervical Cancer Mortality in Geographically High-Risk Populations. Research is needed to determine why, despite a three-fold reduction in cervical mortality nationwide in the past 50 years, counties stretching from Maine southwest through Appalachia to the Texas/Mexico border, in many Southeastern states, and in the Central Valley of California have experienced persistently higher cervical cancer mortality rates. To address this 50-year disparity – for a cancer from which no woman in this Nation should die – NCI and its national, state, and local partners are working to: (1) synthesize research knowledge, (2) identify core findings, (3) articulate program and policy options, and (4) disseminate this information to Federal, state, and local policy makers.

Human Papillomavirus (HPV) Clinical Trials in Costa Rica. Comprehensively controlling the human papillomavirus would virtually eliminate cervical cancer, which disproportionately affects economically and socially disadvantaged women around the world. For the past 2 years, NCI has been following the medical condition of more than 5,000 women in Guanacaste, Costa Rica, who are enrolled in a randomized clinical trial to (1) evaluate HPV DNA testing and visual and automated cytology techniques and (2) determine the optimum strategy for managing low-grade cervical abnormalities. An HPV vaccine trial to compare the efficacy of two vaccines developed by the NCI is now underway in Costa Rica. From 15,000 to 20,000 women will be

invited to participate in the trial, which is expected to run for the next 8 years.

Cancer Survivorship in Minority and Underserved Populations. Investigators at NCI-supported Comprehensive Cancer Centers are using supplemental funding to examine:

- The physical and psychosocial needs of medically underserved cancer survivors and/or their families and how these needs compare with those found in cancer survivors and/or their families from majority populations
- Sociocultural variables that affect cancer survivorship, particularly those that affect quality of life
- The nature and effectiveness of existing post-treatment medical and support services designed for cancer patients from underserved communities
- The effectiveness and feasibility of behavioral measures and interventions aimed at assessing and reducing secondary physical and psychological consequences in minority or underserved cancer survivors and their families

See also page x for a report on the Digital Divide Pilot Projects initiative through the Cancer Communications Extraordinary Opportunity.

The Plan – Reducing Cancer-Related Health Disparities

Goal
Understand the causes of health disparities in cancer and develop effective interventions to reduce these disparities.

Objectives and Milestones for Fiscal Year 2003

1. **Create and implement a comprehensive plan for NCI activities in health disparities research, education, training, and health services support.**

- Expand the capacity of the NCI Center to Reduce Cancer Health Disparities to support NCI health disparities research opportunities.
- Disseminate findings on the relationship between race and cancer care in three areas:
  - The cost of untreated cancer to society among newly diagnosed uninsured cancer patients
  - The cost/benefit of extending Medicare coverage to all newly diagnosed cancer patients without insurance
  - The influence of the concept of race on basic scientific inquiry and on translational, clinical, and public health research
- Further develop and implement NCI's integrated low-literacy program by customizing materials with cultural and language appropriateness for different audience groups.

2. Improve capacity and accelerate knowledge through fundamental cancer control and population research.

- Develop Interdisciplinary Centers on Cancer and Society to:
  - Expand understanding of the social and environmental determinants of cancer and the psychosocial, behavioral, and biologic factors that mediate them.
  - Develop hypotheses for cancer control research at social, institutional, and policy levels.
  - Develop, apply, and evaluate interventions to improve cancer outcomes and reduce outcome disparities.
- Expand epidemiologic investigations to explore racial and ethnic cancer disparities with a focus on cancers for which these disparities are greatest (e.g., breast, cervix, kidney, prostate).
- Support research on the biologic variability in cancer in terms of tumor aggressiveness, differential response to therapy, genetic polymorphism, and psychoneuroimmunologic factors as mediators of social environment.
- Build on findings from the Prostate Cancer Outcomes Study to examine risk factors associated with late-stage disease – lifestyle, biological and clinical characteristics, and access to care – while accounting for state-of-the-art measures of socioeconomic status.

3. Expand our ability to define and monitor cancer-related health disparities.

- Develop new data collection methods for socioeconomic and cultural factors including measures, data sources, and data linkage.
- Examine informed consent provided with prostate cancer screening and treatment in different age, race-ethnicity, and socioeconomic groups as a measure of quality of care in situations where there is uncertainty about the efficacy of interventions.
- Conduct methodological evidence-based research to ensure that survey, epidemiological, and clinical research involving cancer risk factors exhibits cross-cultural equivalence.
- Enhance use of the NCI *Cancer Progress Report* process to monitor health disparity reductions and reach Healthy People 2010 goals.

4. Expand cancer control intervention research in prevention, early detection, treatment, and communications.

- Expand the developmental research grant support for the Special Populations Networks for Cancer Awareness Research and Training program.
- Collaborate with the Centers for Disease Control and Prevention to support new intervention research on barriers to screening for women who underuse or never use breast and cervical screening and on sociocultural determinants in planning, implementing, and evaluating these interventions.

- Develop formal affiliations between NCI Cancer Centers and Minority-Serving Institutions.
- Provide supplemental funding to Cancer Centers for health disparities research, to reduce the heaviest cancer burdens among disadvantaged populations, address disparities in risk factors, access to prevention interventions (e.g. smoking cessation, dietary change, physical activity), quality cancer care, and clinical trials.

5. Reduce outcome disparities in special populations by increasing access to state-of-the-art clinical trials in cancer prevention and treatment.

- Expand Clinical Trials Outreach Programs to increase participation by underrepresented populations; establish clinical trials units at historically black and other minority medical institutions; strengthen clinical trials units at minority-based community oncology sites.
- Increase clinical trials participation by minority physicians and health professionals by implementing an NCI fellowship training program in clinical trials for minority physicians and forums for minority scientists' input into developing clinical trials that address issues of special importance for minority and special populations.

6. Expand the channels for research dissemination and diffusion.

- Expand support for advanced training of state health department staff and American Cancer Society volunteers in best practices for using surveillance and intervention evidence data in comprehensive cancer control planning.
- Establish and maintain local and regional partnerships to understand and overcome cancer control infrastructure barriers that contribute to health disparities.
  - Establish new comprehensive cancer control program initiative with the Washington, D.C. Department of Health.
  - Develop and demonstrate approaches for bringing the latest interventions in cancer screening, care, and treatment, including access to clinical trials, to Native American populations through national and regional Indian health boards, tribal organizations, the Indian Health Service, and established Native American investigators.
- Fund supplements to NCI research grants for dissemination of evidence-based interventions specifically aimed at reducing health disparities.

7. Expand minority investigator competition for and minority population involvement in health disparities research.

- Recruit two additional minority scientists and physicians to the Cancer Prevention Fellowship Program to specifically focus on health disparities research.
- Fund 30 new cancer education grants dedicated to the continuing education of physicians in and outreach and education programs for underserved and

minority communities, as well as to the accrual of minority and underserved populations to NCI-sponsored clinical and prevention trials.

- Develop community-based participatory research in cancer control through partnerships with NCI-funded Comprehensive Cancer Centers, Special Populations Networks, and Minority-Serving Institutions.

Informatics and Information Flow

The Challenge

The study of *informatics* involves determining how to best manage information using computer and statistical techniques. NCI needs innovative informatics systems to ensure that the flood of information stemming from the rapid pace of scientific discovery is available to those who need it. An example from human genetics research highlights the breadth of the cancer informatics need. The approximately 30,000 human genes within the human genome, along with millions of variations that can exist in these genes, have been mapped, cataloged, and made available to cancer researchers. Furthermore, there are data to show how a number of genes can be expressed differently among thousands of different cancers. To add to the information on the genes themselves, the number of drugs targeted to interact with certain genes and related proteins is multiplying every day. Other areas of cancer research are equally productive, generating a comparable avalanche of information. How does any individual cancer researcher access and make sense of this large and complex collection of data? NCI's challenge is to develop informatics systems to integrate and share this knowledge and to use it to improve the treatment and delivery of care to cancer patients.

We envision meeting this challenge with a Cancer Informatics Infrastructure (CII) composed of three interrelated components. The first is a standards-based knowledge management framework, which provides structure and consistency to the CII. The second component consists of information technology tools, which link to the framework and allow the capture, analysis, application, and re-use of information. The third component is made up of people – a collection of experts from diverse areas of scientific research, including informatics – who are empowered to apply these tools to problem solving in the realm of cancer research and care. This three-component CII will create electronic interfaces among cancer researchers, reaching and connecting basic, translational, clinical, and population-based research communities.

The purpose for this infrastructure to increase the efficiency of cancer research and integrate information critical for the generation of knowledge. Attaining this goal will require the involvement of the entire cancer research community, including strategic partnerships with interested commercial, academic, and other governmental groups, thus broadening the base of interoperable tools, data, and infrastructure. We must have scientists in place to broker the application of this infrastructure in the diverse fields of cancer research. Once established, we must provide mechanisms to ensure that the infrastructure can evolve to reflect the ever-changing research landscape and provide for cross- training of scientists, thus bridging the gap between the informatics and biomedical research communities. Ultimately, this infrastructure will unify the cancer research and care communities by enabling efficient, comprehensible, and easy access to the diverse collections of cancer knowledge, thus facilitating the rapid translation of research observations into clinical and public health interventions.

Progress Toward Meeting the Challenge

NCI has made much progress in creating and implementing its informatics system. Our progress includes the following important achievements.

Standards-Based Knowledge Management

NCI's **Center for Bioinformatics (NCICB)** (http://ncicb.nci.nih.gov)as established in 2001 to provide standardized bioinformatics support and integration of NCI's diverse research initiatives. The NCI thus provides for the seamless progression of investigative efforts from the level of molecular biology and molecular genetics, though pre-clinical animal modeling of identified molecular targets, to the informed design of clinical trials and the integrative weaving of this information into the rich tapestry of knowledge required to address the difficult problems in cancer research and care.

Through the NCICB, NCI has developed and put into use *common data elements* – standard ways of referring to scientific phraseology – for breast, prostate, lung, and colon cancer, and for leukemia, and has provided electronic interfaces among our cancer research communities to facilitate information exchange. For example, the NCI Enterprise Vocabulary Services (EVS) supports easy, user-friendly access to diverse collections of cancer knowledge. This serves basic, translational, clinical, and population-based science communities by organizing and translating their respective distinct, but overlapping, terminologies. One database is used for translating between vocabularies used by different scientific specialties, and another builds a common vocabulary. Other EVS services include multiple vocabulary browsers, document index services, and software and technical support to integrate EVS databases and tools with other informatics systems. All of these services greatly enhance the capabilities of NCI staff and collaborative groups that increasingly use them.

In another effort, we are building a standards-based repository to comprehensively store the data used by all our programs in adherence with the international standard for data elements used by many other Federal organizations. This keystone effort will ensure that common data elements in our clinical trials and animal model programs are readily available for sharing with all NCICB-supported programs.

NCI realizes the importance of making informatics data maximally accessible and easy to use. To ensure that the needs of the cancer community are recognized in the standards-setting process, the NCICB has joined several national standards bodies. To make cancer data easier to access, the Center is creating a large data repository designed to simplify access to much of the data held by NCI. We are also working to create a unified national repository of health-related meta-data, compliant with international standards. Recurring seminars keep NCI and the public up to date on developments in informatics techniques, practices, and standards.

The four inter-related research initiatives supported by the Center represent key areas of knowledge in cancer research, and they attest to the success of the NCI's Informatics program to date. The NCICB supports and integrates the efforts of these four initiatives with one another and with the larger cancer community, maximizing their potential impact on cancer research and care.

- NCI's Clinical Trials (http://lpgprod101.nci.nih.gov:8080/trials) infrastructure is the product of NCI's first application of its developing CII, successfully applying the emerging infrastructure to concrete improvement in cancer research and care. The new infrastructure has increased information sharing between many clinical trials and with other types of research efforts and has helped researchers to organize and launch clinical trials faster and run them more efficiently. From these important beginnings we extended the infrastructure to support the efforts of other areas of cancer research.

- The Cancer Genome Anatomy Project (CGAP) (http://cgap.nci.nih.gov)the *gene expression profiles*– how the same gene can function differently depending on certain factors, in this case disease state – of normal, precancer, and cancer cells. The goal is to use the gene expression profiles to improve detection, diagnosis, and treatment. The CGAP informatics team has made dramatic strides in making genomic data from the broader scientific community easily available to cancer researchers in a format familiar to them. CGAP's use of informatics supports cancer research by providing integration of cancer genetics information not easily accessible elsewhere.

- Mouse Models of Human Cancer Consortium (MMHCC) (http://mmhcc.nci.nih.gov) is a collaborative program that designs *mouse models* of human cancer - strains of mice that are specially suited for the study of human cancer - and makes them available to the research community. NCICB has been instrumental in providing critical information and tools to MMHCC researchers and quickly integrates the results of MMHCC efforts into the cancer community.

- The Director's Challenge – Towards a Molecular Classification of Cancer is a challenge issued by the NCI Director in 1998 (http://dc.nci.nih.gov) to apply molecular technology to create ways of classifying tumors based on distinguishing molecular characteristics; this provides the framework to better understand and study different cancers. The success of this effort is integrally dependent on NCI's informatics technology tools and the provision of standardized information flow to and from other NCI initiatives and the greater cancer community.

NCI Cancer Informatics Technology Tools

A diverse array of NCI informatics tools is promoting the efficient, expeditious, and safe delivery of effective cancer agents to the American public. **Business support tools** have been implemented **to streamline procedures and processes and to eliminate redundancy in the clinical trial system**. This effort has reduced the administrative burden on researchers, dramatically enhancing program efficiency. Use of these tools has permitted stable staffing requirements, which is notable in the face of increasing, sometimes doubling, workloads.

NCI has developed **informatics tools to ensure clinical trial safety**. Our standardization of business rules and toxicity terminology has improved reporting and assessment of previously unknown or severe toxicities from NCI-supplied investigational drugs. Success was such that the oncology community has asked that the improvements be applied to non-NCI cancer agents and to other research areas (e.g., AIDS trials, cardiovascular disease, and drug abuse).

NCI is developing **integrated informatics applications to promote scientific planning**. These tools are flexible and scalable to help databases remain current as new therapies and further advances in cancer biology are discovered. The applications aid researchers in: planning use of sophisticated oncology agents designed to attack specific molecular targets; refining cancer agents based on pre-clinical and mechanistic data; reallocating staff to areas of scientific importance; and recruiting minority participants into clinical trials.

NCI is focusing on all aspects of **software development for scientific management systems**. We have introduced a process to manage all phases of NCI software development to create a complete software development life cycle. This project maximizes the effectiveness of the spectrum of NCI resources, including information flow, human resources, grant management, and space management.

Informatics for Cancer Research and Care

NCI's Net-Trials™ demonstrates a comprehensive implementation of informatics to serve the clinical trials cancer community. Net-Trials™ is a Web-based clinical trials information system that supports every aspect of the protocol life cycle, including information management, data analysis, and secure Internet access allowing *real- time collaboration* – interactive collaboration without time delay – of multiple centers. Net-Trials™ streamlines operations and improves data quality, patient safety monitoring, and analysis of much larger groups of data across the entire clinical trials portfolio. Still under development, Net-Trials™ is being used by at least six clinical branches of NCI's Center for Cancer Research. Plans include expanding it to include all intramural clinical studies and perhaps beyond; it has been piloted at several sites outside NCI's intramural program. As one of the early tools in the informatics toolbox, Net-Trials™ is expected to help NCI link basic, translational, and clinical research efforts and codify and implement the evolving standards for the conduct of

clinical research.

The Plan – Informatics and Information Flow

Goal

Create a cancer informatics infrastructure that enhances information and resource exchange and integration among the diverse collection of basic, clinical, and population science researchers, thus facilitating cancer prevention, translational diagnosis, and treatment investigations.

Objectives and Milestones for Fiscal Year 2003

1. **Through the NCI Center for Bioinformatics (NCICB), expand NCI's backbone informatics infrastructure to enable support and integration of NCI-supported basic, clinical, translational, and population research initiatives.**

- Expand the NCICB to provide additional support, enhance integration of data and development of tools emanating from NCI's Extraordinary Opportunities, and facilitate information exchange within and between NCI-supported research initiatives. Deploy an additional NCICB module to support the Cancer Molecular Analysis Project's specialized bench-to-bedside information integration and display needs.
- Establish a toolbox of open-source informatics applications and services based on a common set of operating principles and standards that support diverse cancer research activities, including those emanating from NCI Extraordinary Opportunities.
- Develop a research infrastructure that exploits and institutionalizes the use of a "standards stack," assembling common vocabulary, standard data elements, and information models to further the exchange of all types of cancer information and data among the cancer community.
- Expand the informatics backbone infrastructure by increasing information technology-based support services to facilitate and enhance planning, execution, and communication of the diverse research portfolio supported by NCI.

2. **Create a community matrix of interoperable data sources, analytic tools, and computational resources that provide an extensible plug-and- play informatics capability for the cancer research community.**

- Expand the informatics capacity of the larger cancer research community with partnerships to develop a standards-compliant infrastructure that can be plugged into the backbone and each partner's information. Establish a minimum of five academic, Government, and commercial strategic partnerships, providing a research park setting where NCI scientists and

partners can work together to address bioinformatics questions.

- Through a minimum of 20 investigator-based awards that build on the NCI informatics backbone:
  - Deploy the matrix of standards-based resources to the cancer research community to serve as the foundation on which additional infrastructure is constructed.
  - Facilitate rapid deployment of related new research initiatives.

3. Expand the cancer research community's capacity to perform informatics research on a local institutional basis.

- Establish a network of bioinformatics research centers to work with and through the NIH Biomedical Informatics Science and Technology Initiative, using a novel interdisciplinary management team to select and coordinate the centers.
- Expand standards-compliant institutional infrastructure by providing infrastructure supplements to NCI-supported research organizations, supporting the growing need of investigator-initiated research to access state-of-the-art biocomputing tools and data.
- Promote informatics training by encouraging recruitment of new scientists and cross training in a variety of life science research domains through 20 development and transition awards.

Cancer Research Training and Career Development

The Challenge

Training and career development for the next generation of scientists remains one of our most important challenges. The scientists of the future will need to be more versatile in their use of new technologies, able to work in teams to understand the complicated environmental, lifestyle, genetic, and molecular variables contributing to human cancers, and better prepared to translate discoveries into public benefit. We need to implement and sustain multiple long-term strategies to attract the most talented individuals to cancer research. We need to create a stable cadre of well-trained technical, biological, behavioral, medical, and public health scientists dedicated to the cancer research enterprise. And, as the interdisciplinary environment increasingly becomes a way of life for researchers, we need to ensure that scientists can and will work together effectively to solve problems.

Our success will depend upon our ability to move beyond traditional educational and research cultures, overcome health financing constraints, and address socioeconomic inequities that have proven to be barriers to progress in the past. The theme for the future is to train scientists to work on problems as integrated, multidisciplinary teams.

To meet these challenges, we must continue to implement training and career development strategies to address a number of crucial issues. We must:

- **More adequately prepare basic scientists and provide them with more attractive career paths.** By providing basic scientists in training with the background to conduct research directly related to human cancer and preparing them to collaborate with clinical and population scientists, NCI can provide them with the skills to be successful contributors to cancer research teams. Moreover, increasing trainees' stipends to levels more reflective of their education and skills will help ensure that careers in basic science will continue to remain attractive.
- **Reverse the migration of talented and creative physicians from research to practice.** This is the single most threatening consequence to cancer research from the shifting economics of the health care system. We must use more effective means to train clinical investigators and ensure they have protected time to conduct the patient-oriented research that ultimately will translate basic discoveries into better methods for cancer prevention, diagnosis, and treatment. These investigators must receive the necessary intensive training and education that guarantees informed consent and provides maximum safety for patients participating in research.
- **Increase the numbers and stabilize the careers of cancer prevention, control, population, behavioral, and public health scientists.** The discoveries of scientists dedicated to prevention, early detection, behavior modification, and risk factor analysis will have a major impact on reducing future cancer incidence and mortality. We must develop better ways to train these scientists to function in interdisciplinary research settings and work effectively with patient-oriented and basic scientists. We also must

provide these scientists with protected time in which to conduct research.

- **Create a research community that is ethnically and racially diverse.** We need scientists who are particularly sensitive to the factors that lead to disproportionate cancer incidence and mortality in underserved populations and who are prepared to conduct research that will help overcome the cultural and socioeconomic barriers responsible for the unequal burden of cancer.
- **Attract and integrate technical and informatics experts into cancer research.** Specialists in these disciplines are likely to provide a critical driving force for future progress.

Progress Toward Meeting the Challenge

A variety of individual and institutional training and career development awards are being employed to meet the needs of new and established investigators and NCI's anticipated research priorities. Special programs have focused increased resources on career tracks for M.D.s in cancer research, behavioral and population scientists, minority scientists, and scientists in highly technical fields important to the future of cancer research. Education programs for health practitioners and the public are being more effectively integrated and made accessible through improved national networking and exploitation of informatics technologies.

Individual Awards

- **Individual National Research Service Awards** continue to provide a stable cadre of well-trained basic scientists.

- **Individual mentored 5-year awards** provide special opportunities for M.D.s in basic or clinical research and for individuals pursuing cancer prevention, control, behavioral, and population science. Interest in these awards has increased dramatically over the last 2 years, resulting in a three-fold increase in the number granted – evidence of both the need for and effectiveness of these programs.

- **Bridging awards** encourage basic scientists and minority scientists to pursue careers in cancer research. These awards require recipients to undertake mentored and independent research, providing them protected time to develop independent research programs. These special bridging awards have increased steadily since their inception 5 years ago and are on target for achieving their strategic objectives.

- **Transition awards** provide for 3 years of protected time following mentored postdoctoral training or for new investigators to initiate successful research programs. These awards are now in place for NCI's two most critical areas of need: medically trained doctors in basic and clinical research and population scientists. A new transition award is now available for minority scientists. Because we have not been able to achieve

our targeted objectives for transition awards during their first few years, we are taking new measures to increase their accessibility and attractiveness.

- **Established investigator awards** provide seasoned investigators in the clinical sciences and in cancer prevention, control, behavioral, and population sciences protected time to conduct research and mentor new scientists. The number of these awards has increased since their introduction, and their availability appears to be helping to curtail the migration of physicians from research to patient care.

- **New diversified sciences career development awards** attract technology developers and scientists in disciplines not traditionally associated with cancer research but clearly needed for the future.

Institutional Awards

Institutional awards are 5-year awards for developing and conducting training and career development programs. These awards achieve special goals by establishing specific requirements and assembling mentors whose skills support program objectives.

- **National Research Service Awards**, NCI's mainstay for training basic scientists, include special provisions for curriculum and research environments that expose all trainees to cancer-related opportunities and important new research approaches of the future.

- **Institutional Clinical Oncology Career Development Programs** prepare the next generation of clinical scientists to design and implement hypothesis-based clinical trials and to collaborate with basic scientists. There are now nearly 20 of these programs in place throughout the nation.

- **Institutional Education and Career Development Programs**, initiated in 2000, prepare participants for collaborative, multidisciplinary team research settings. This program is proving to be extremely successful in meeting NCI's strategic needs by stimulating the initiation of new, forward-looking training programs in prevention and control, imaging sciences, outcomes research, and molecular pathology.

- The **Continuing Umbrella of Research Experiences Program** engages minority high school and undergraduate students and provides them with assistance through all stages of training and career development needed to become independent investigators.

- **Minority Institution/Cancer Center Partnerships** have the potential to link over 300 Minority-Serving Institutions (colleges and universities whose enrollments include a significant proportion of students from minority groups that are underrepresented in science) with NCI Cancer Centers to increase the number of minority students engaged in cancer research; strengthen the research capabilities of minority institutions; and support

Centers in reducing cancer incidence and mortality in minority populations. Several comprehensive partnerships are now operating, and numerous planning activities are being supported to enhance more focused collaborations between NCI Cancer Centers and minority-serving institutions.

For more information on these programs and career tracks, go to http://cancer.gov/cancertraining.

The Plan – Cancer Research Training and Career Development

Goal

Build a stable, racially and ethnically diverse cadre of basic, clinical, behavioral, and population scientists trained to work together effectively and to use the most advanced technologies in building our knowledge base and in translating discoveries into more effective cancer prevention, detection, diagnosis, and treatment strategies.

Objectives and Milestones for Fiscal Year 2003

1. **Continue to provide training, career development opportunities, and protected research time to developing and established cancer scientists.**

- Maintain a stable National Research Service Award (NRSA) program to train pre-doctoral and post-doctoral basic scientists through traditional institutional and individual awards. Increase the stipends of trainees by 10 percent in order to make research careers more attractive.
- Continue to increase the participation of clinically trained individuals in basic research and in patient-oriented research by funding 20 new individual mentored awards, 20 new transition awards, and 10 new established investigator awards.
- Continue to expand the number of well-trained population, behavioral, and public health scientists in cancer research by funding 20 new individual mentored awards, 15 transition awards for junior independent scientists, and 10 awards to established investigators.
- Expand the role of the NCI Intramural Program in training extramural investigators by funding five additional trainees in the NCI Scholars Program and by creating two new intramural training and career development programs that partner and network with extramural institutions and focus on underdeveloped areas that can benefit by integrating sparse resources (e.g., radiation oncology, informatics, prevention).

2. **Continue to provide and refine special training and career development opportunities that prepare new and established scientists to function in collaborative, team research settings and that integrate new technical disciplines into the cancer research enterprise.**

- Increase the number of basic scientists who focus on human cancer research and who can collaborate effectively with clinical and population scientists in translational research by funding 30 new special bridging career awards.
- Fund five new Institutional Clinical Oncology Career Development Programs to prepare clinically trained individuals to become expert in all aspects of clinical trials design and implementation as well as effective partners of basic scientists in moving discoveries in the laboratory to improved clinical tests and therapies.
- Implement 10 new Institutional Career Development Programs for training scientists to work in highly complex team research settings involving investigators from diverse disciplines.
- Support five new individual Diversified Sciences Career Development Awards to attract new disciplines (e.g., physics, engineering, informatics) into multidisciplinary cancer research settings.
- Expand and initiate career development opportunities in highly specialized interactive, translational, and research consortia and networks (e.g., Specialized Programs of Research Excellence, Imaging Centers, Tobacco and Tobacco-Related Centers) that are accessible to new and established investigators.

3. Expand programs to recruit, train, and sustain underserved racial and ethnic minority individuals in cancer research and provide partnership opportunities for training and career development.

- Expand the Continuing Umbrella of Research Experiences (CURE) Program by: increasing the number of trainee positions on institutional NSRAs by 50; providing new supplemental funding to 10 cancer centers for high school and undergraduate student research experience; funding 10 new minority training positions in Clinical Oncology Career Development Programs; funding 10 new positions for Cancer Education and Career Development Programs in the population sciences; funding 50 new Minority Investigator Supplements to NCI research project grants; funding 20 new mentored career development awards for basic scientists and clinically trained scientists; and funding 10 new Career Transition Awards for basic, clinical, behavioral, and population minority scientists in their first junior faculty positions.
- Promote collaborations between scientists and educators in MSIs and in NCI-designated Cancer Centers through 15 planning grants for developing MSI/Cancer Center research training programs for minorities and outreach education programs for minority communities.
- Increase minority access to training and career development opportunities by improving NCI Internet information services, establishing linkages between public and private agencies that provide related services, and establishing 20 new positions in NCI Cancer Centers that will "broker" the connections between minority individuals seeking research experiences and Cancer Center scientists.

- Integrate the NCI CURE Program and the NCI Minority Institution/Cancer Center Partnership Program more effectively into the Minority Biomedical Support Grant Program in the National Institute of General Medical Sciences.

Extraordinary Opportunities for Investment

NCI's "extraordinary opportunities for investment" are broad-based, overarching areas of scientific pursuit that hold tremendous promise for significantly expanding our understanding of cancer. With focused efforts and increased resources in these areas, we can build on past successes and technological breakthroughs to stimulate dramatic progress in addressing some of our most difficult questions. Although the needed resources are not trivial, our failure to respond quickly with investment in all of these areas will slow the pace of cancer research at all levels and impair our ability to find better ways to care for those whose lives are touched by cancer.

NCI seeks formal input from cancer experts representing a broad spectrum of perspectives to help identify these areas of exceptional promise. Every three years, we ask members of the research community, advisory groups, and advocacy organizations to revisit the "extraordinary opportunities" and recommend important areas of research into which additional resources should be infused over the next three-year cycle. We thoroughly assess these responses, blend related ideas, and, with our advisors, select new investment areas. The current six extraordinary opportunities were first outlined in NCI's Fiscal Year 2001 budget proposal and are continued in this proposal for Fiscal Year 2003.

The purpose of the extraordinary opportunities is to identify areas of discovery that build upon important recent developments in knowledge and technology and that hold promise for making significant progress against all cancers. Extraordinary Opportunities must involve approaches to cancer research beyond the size, scope, and funding of our current research activities, be implementable with specific defined investments, and be described in terms of achievable milestones.

These investment areas lead to new research awards, new or expanded programs, and collaborations, all activities that help us improve prevention, detection, diagnosis, and treatment for all cancers.

Genes and the Environment

The Opportunity

As we better understand the interplay between inherited susceptibility to cancer and environmental risk factors, we will be able to develop more meaningful approaches to cancer prevention, early detection, and treatment. Until recently, we have pursued separate lines of inquiry for cancer genetics and environmental risk factors for cancer. As such, we have been able to identify some of the human genes that make people susceptible to cancer, to apply increasingly sophisticated molecular technologies to analyze genetic changes, and to examine the relationship between disease development and individual genetic profiles. We have learned about a variety of carcinogenic environmental factors not only in the outdoors but also in the home and workplace. These include pollutants in air, water, and soil; components of food, tobacco, alcohol, and drugs; sunlight and other forms of radiation; and infectious agents.

Early efforts to discover how genes and environmental factors interact to cause cancer are showing promise but also highlight the complexity of the puzzle. Some genes have proven to be so powerful that their presence in an individual makes cancer highly predictable. For example, carriers of the gene for Familial Adenomatous Polyposis are almost certain to develop colon cancer. But an inherited predisposition to other types of cancer requires other factors for cancer to occur, such as the presence of other genes or exposures to chemicals in the environment. For example, breast cancer development in women carrying mutations in the susceptibility genes BRCA1 and BRCA2 is likely but uncertain and may be related to a combination of factors. Similarly, some environmental exposures – tobacco use, for example – can be strong, but not certain, predictors of cancer.

NCI's opportunity is to uncover elements of the gene-environment interaction that can lead to tangible improvements in our ability to prevent and control cancer. For example, we expect to identify previously unsuspected carcinogens through the study of newly discovered genes that predispose people to cancer. We also want to learn how certain environmental exposures increase the cancer risk for genetically susceptible subgroups. When we can define the cancer risks associated with specific environmental and genetic factors and their interactions, we can develop new individual and public health strategies to avoid adverse exposures, check genetic susceptibility earlier, identify appropriate treatment regimes, and take special precautions for people at high risk.

To progress in this area, NCI needs to develop new ways to study cancer genetics, environmental exposures, and their interaction and to maximize the availability and use of large amounts of research data and other resources. Large-scale studies that require new levels of cooperation and innovation from the cancer community will be needed to achieve tangible improvements in medical practice and public health.

Progress in Pursuit of Our Goal

NCI is pursuing research opportunities in five growth areas to better understand cancer-related genes, environmental factors, and their interaction. First, we are ***building the capacity*** to understand genetic variation, identify important biologic exposures, and explore the complex interaction among them through research partnerships.

- Investigators already involved in 15 separate prospective[3] studies of large population groups are pooling high quality environmental exposure data along with tissue, blood, and other body fluid samples suitable for genetic analysis to form a combined study size of 700,000 participants, large enough to yield significant findings. Some members of this **Cohort[4] Consortium** of investigators are involved in a collaboration to uncover gene-environment interactions by compiling and examining more than 7,000 cases each of breast and prostate cancer.

- Two other groups of investigators are using the case-control[5] approach to identify genetic and environmental determinants of non-Hodgkin's lymphoma (NHL) and brain cancer. These **Case-Control Consortia** of investigators are pooling data from more than 5,000 patients with NHL and more than 3,000 with brain tumors.

- Two groups of researchers are partnering to collect high quality cancer registry data on environmental exposures of patients and a variety of biologic specimens from these patients for use in genetic analysis. These data and analyses will be compared with those of non-cancer patients, and the resulting information will serve as a resource for the research community in its search for susceptibility genes and environmental carcinogens.

Second, NCI is examining a ***broad spectrum of approaches to assess and measure environmental exposures***.

- **Non-invasive methods for detecting cancers, carcinogenic exposures, and genetic susceptibility** can ease the stress on patients and make screening for environmental exposures and early signs of cancer more thorough and affordable. These methods also are well suited to use in large-scale research studies. Researchers are examining options that would allow doctors to screen for lung cancer by testing for the presence of a molecular marker in sputum samples; sample DNA from cheek cells removed from inside the mouth; use saliva samples instead of blood to test for body nutrient levels, hormones, and environmental chemicals; or use urine samples to validate patient responses to questions about dietary habits.

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[3] *Prospective* means that, for the most part, the people are cancer- free at the start of the study.

[4] A *cohort* is a group of people who are followed over time in a research study.

[5] A c*ase-control* study compares people who already have cancer against people who do not have cancer.

- New and easier methods, such as biodosimetry and direct versus surrogate measures, may provide **new options for the assessment of difficult-to-measure environmental exposures**.

- Collaborative studies with the National Institute for Occupational Safety and Health are **improving assessment measures for studying** cancer resulting from **exposure to low-dose radiation and agricultural pesticides**. Sophisticated monitors designed for workers in specific occupations can be used in large groups of workers.

- **Techniques using geographic information systems** to support the Long Island Breast Cancer Study of complex toxicological and environmental exposures and breast cancer incidence can be applied to other areas of research as well.

Third, we are ***advancing research to discover and characterize cancer pre-disposing genes*** by building on NCI-supported cancer family registries and promoting collaborations among investigators who have studied large numbers of families with cancer.

- The **Cancer Family Registry (CFR)**, a large international registry of more than 8,500 ethnically diverse families and 21,000 participants, focuses on highly penetrant breast and ovarian cancer genes by recording information on cancer family history, demographics, environmental and lifestyle risk factors, and clinical data and by maintaining a bank of biological specimens. The CFR is supporting several studies to provide the information needed to make prevention and treatment decisions. One such study examines the effects of hormones as well as diet, body size, physical activity, alcohol consumption, and radiation on breast cancer risk among carriers of BRCA1 and BRCA2 mutations.

- A second large resource, the **Colon Cancer Family Registry**, has assembled data on more than 5,000 families, including more than 150 families with hereditary non-polyposis colon cancer and more than 300 with two or more first-degree relatives who have the cancer.

- Other groups of investigators are working to discover and characterize highly penetrant familial genes associated with melanoma, ataxia telangiectasia, and prostate and lung cancers.

Fourth, NCI is ***supporting the development of a number of tools for use in gene discovery and characterization***. These efforts are needed to advance our understanding of gene-environment interactions and the application of that knowledge.

- Through the **Mouse Models of Human Cancers Consortium (MMHCC)**, scientists are capitalizing on the remarkable correspondence between the human and mouse genomes to identify human cancer-related genes and are facilitating rapid cancer gene discovery by adding mouse models of known familial cancer susceptibility genes. In collaboration

with population scientists studying cancer families, MMHCC researchers applied a new timesaving strategy of mouse cross-breeding to quickly pinpoint the BRCA1 breast cancer susceptibility gene. The mouse studies soon revealed the function of the gene and enabled scientists to verify its role in altering susceptibility to breast cancer. Furthermore, a model for the gene PTEN/MMAC1 may shed light on several types of cancer, including Cowden disease, a syndrome that predisposes family members to breast, brain, prostate, endometrial, and bladder cancers.

- NCI used a risk assessment model that combines several known risk factors in the Tamoxifen Breast Cancer Prevention Trial. The success of the model exemplifies how we can substantially increase our ability to predict breast cancer risk. Scientists have greatly expanded information on risk factors among African American women and are incorporating data from the Women's Health Initiative Trial. Using this **Gail Model** as a pattern, researchers are now constructing models for both ovarian cancer and colorectal malignancies built on pooled data from large multi-center studies.

- Through the efforts of the **Genetic Annotation Initiative (GAI)**, the genetic information generated by the Cancer Genome Anatomy Project (CGAP) is being made available for research use. More than 35,000 gene-based polymorphisms – DNA variations among individuals – have been identified, and GAI scientists have established high-throughput laboratory assays to detect more than 7,000 of these variants. As with all of the CGAP resources, materials are available free of charge through the World Wide Web (http://cgap.nci.nih.gov). Scientists can use these tools to investigate the roles of these genes in families and populations.

Fifth, NCI ***has established a productive infrastructure to support intervention trials on inherited susceptibility to cancer.*** Such trials are vitally important to improving our ability to detect and treat cancer earlier. Through the **Cancer Genetics Network (CGN),** researchers are conducting a number of these studies. 1) A pilot study of an early detection technique for ovarian cancer screening in genetically susceptible women involves a CGN partnership with several NCI-supported programs, including the Gynecologic Oncology Clinical Trials Group. 2) In another CGN study, researchers are comparing the effectiveness of several existing biostatistical models for estimating breast cancer risks. 3) Another group is developing innovative analytical methods to identify colon cancer genes that are as yet undiscovered. 4) A pilot study will improve methods for recruiting and retraining individuals and families at high risk of cancer into clinical trials. 5) Finally, a pilot collaborative is coordinating a multi-institutional study of genetic and environmental modifiers of cancer risk in women with BRCA1 & 2 mutations.

To apply the latest findings in human epidemiologic and clinical investigations, the CGN is extending its network of collaborations and infrastructure resources to promote active collaboration with the Mouse Models of Human Cancers Consortium, the Genetic Annotation Index, and the Cancer Genome Anatomy Project. In addition, CGN is collaborating with the NCI Special Populations Networks for Cancer Awareness Research and Training to ensure wider opportunities for people from diverse communities, including

investigators representing those communities, to participate in research on genetic susceptibility to cancer.

The Plan – Genes and the Environment

Goal

Discover genetic, environmental, and lifestyle factors and their interactions that define cancer risk and that can inform the development of new strategies for prevention, early detection, and treatment.

Objectives and Milestones for Fiscal Year 2003

1. **Identify new environmental risk factors and susceptibility genes and determine their interactions in cancer causation.**

- Utilize the unique advantages of the Cohort Consortium to investigate exposures best studied prospectively in large populations and their interactions with susceptibility genes.
  - Continue the five-center gene-environment risk factor discovery study of breast and prostate cancers while adding new and innovative studies of other common cancer sites.
  - Expand the number of participants, population diversity, and types of biospecimens.
- Support Case-Control Consortium investigators to address specific gene-environment interactions in detail and establish formal resources for discovery efforts by initiating large population-based and hospital-based studies to develop comprehensive data and specimen resources by cancer site. Encourage use of NCI Atlas of Cancer Mortality and other public use data systems (e.g. Long Island Breast Cancer Study) as source of study from high risk areas.
- Continue improving infrastructure to meet the needs of large, collaborative human population studies.
  - Maximize the utility of specimen resources for human population studies with improved efficiency and cost-effectiveness of specimen collection, processing, storage techniques, and high-throughput assays.
  - Continue developing informatics systems to capture, store, analyze and integrate the massive amount of information generated by these studies.
  - Facilitate the use of new genomic technologies by funding supplements to existing gene-environment focused studies.

2. **Develop new ways to assess and measure environmental exposures for use in population studies.**

- Support development of new methods for characterization of internal dose resulting from complex lifetime exposures.
- Continue expanding NCI's Innovative Molecular Analysis Technologies Program to develop new non-invasive techniques for collecting and measuring DNA and proteins in very small amounts of biologic material.
- Continue support for applying and validating measures of the cumulative cellular, genetic, and molecular effects of environmental exposure through funding supplements for ongoing research programs.

3. Identify cancer-predisposing genes in high-risk families and investigate how other genes and environmental factors modify expression of these genes.

- Fund two new consortia of investigators to identify unknown cancer susceptibility genes (e.g., pancreatic cancer).
- Support interdisciplinary studies for gene discovery and characterization for additional cancer sites by new collaborative family registry groups.
- Support collection of fresh-frozen tumor tissue and other biospecimens from genetically cancer-prone families for microarray-based molecular signature analyses in NCI-supported large population research resources such as a Cancer Family Registry Web site.

4. Develop tools for the study of gene and environment interactions in human populations.

- Extend the Genetic Annotation Initiative to identify new gene variants relevant to cancer in clinically and epidemiologically defined populations, define key molecular pathways by characterizing comprehensive genetic variations on an extended set of gene and protein expression profiles, and develop time and tissue-specific human gene expression profiles from samples with measured exposures to facilitate the identification of epigenetic targets and further define mechanistic pathways of tumorigenesis.
- Augment the Mouse Models of Human Cancers Consortium to more rapidly localize interesting genetic regions, increase the number of models for human hereditary cancer genes, decipher environmental factors that modify cancer development, and test biomarkers for early detection.
- Provide the framework for productive use of genetically engineered mouse models to study human cancer genetics by integrating mouse molecular genetics and human molecular and cataloging mouse single nucleotide polymorphisms to facilitate genotyping of commonly used mouse strains.

5. Support collaborative studies of high-risk individuals to address the clinical, behavioral, and societal issues associated with cancer susceptibility.

- Sustain the Cancer Genetics Network (CGN) as a resource for studies of clinical care for early detection, diagnosis, and treatment of genetically high risk individuals, including those from minority and underserved populations.
- Expand support for studies in cancer genetics that examine psychosocial responses to cancer risk communication within average and high risk populations in order to inform the development of effective educational strategies and resources for patients, providers, and the public.
- Continue to support research in cancer survivorship to evaluate physiologic and/or psychosocial effects of cancer or its treatment among survivors of cancer, and examine the role of genetic factors in these sequelae.
- Refine cancer risk prediction methods/models to integrate genetic and environmental determinants of cancer by developing methods to estimate individual risk. Merge models that are primarily genetic based with those that are primarily environmental. Refine models that predict cancer risk and other outcomes among diverse populations to estimate population burden and policy implications.
- Collaborate with the Centers for Disease Control and Prevention Genomics and Public Health Centers to develop methodological standards specific to the collection and reporting of data from NCI consortia on gene-environment interactions, effectively relating these results to medical practice and public health.

Cancer Imaging

The Opportunity

As recently as 25 years ago, a physician or surgeon who suspected the presence of a tumor in a patient had few options. The normal course of events would be to order x-ray studies to find the tumor's exact location, schedule the patient for surgery, excise a portion of the unhealthy tissue for biopsy, remove the tumor, and explore surrounding tissues to determine if the cancer had spread. But over the last quarter century, improvements in imaging technology have substantially broadened the range of medical options. With the power of imaging technology now available, physicians can get much clearer and more detailed pictures of organs and tissues, and they can view far more than anatomical structures such as bones, organs, and tumors. Using "functional imaging" for the visualization of physiological, cellular, or molecular processes in living tissue, physicians can examine activities such as blood flow, oxygen consumption, or glucose metabolism as they take place.

Modern imaging technology already has had lifesaving effects on our ability to detect cancer early and more accurately diagnose the disease. X-ray mammography, for example, has revealed the presence of very small cancers in thousands of women before the tumors could be detected by physical examination. And computed tomography (CT) can show if a tumor has invaded vital tissue, grown around blood vessels, or spread to distant organs. As the science continues to advance, we will be able to detect changes in the workings of a cell as it becomes malignant and use this information to diagnose cancer earlier.

Eventually, we should be able to tell, in the radiology suite of a hospital, which genes are active in a particular patient's cancer cells, and use that information to choose the best treatment option. In addition to using CT and other imaging technologies to guide treatment choices, scientists have developed methods for combining imaging techniques with radiation sources and high- performance computing. This serves to better target radiation treatments to a tumor's three-dimensional contours, thus minimizing damage to surrounding, healthy tissue. Moreover, with today's technology, we can also identify the molecular characteristics of a tumor and use that information to predict how it will respond to certain treatments. With a visual image of how glucose is being used in cancer cells, we can tell – without the need for a biopsy – how a tumor is responding to a recently administered treatment.

Oncologists also increasingly rely on image-guided therapy, in which imaging is combined with various tumor-killing approaches (toxic chemicals, gene therapy, heat, and cold). By allowing physicians to better distinguish between cancerous and normal tissue and target treatments to diseased tissues, image-guided therapy can minimize surgical trauma, shorten recovery time, improve patients' quality of life, and reduce health care costs.

NCI's opportunity is to further improve cancer imaging technologies with the goal of ensuring earlier and more accurate diagnoses for more cancer patients, reducing the number

of invasive therapies needed to treat their illnesses, and improving physicians' abilities to monitor patients' responses to treatment. With investments in research and development, significant advances in cancer imaging are now possible and will ultimately save more lives.

Progress in Pursuit of Our Goal

As our progress over the last 25 years has amply demonstrated, advances in cancer imaging research and technology have the potential to profoundly affect the practice of oncology and extend patients' lives. With the NCI continuing to focus support on this field, its investment is yielding dividends in the form of tangible further progress in developing better imaging technologies for application in both cancer research and clinical practice.

Developing Better Imaging Technologies and Techniques

- NCI has played a major role in fostering *molecular* or *functional*[6] imaging. Through initiatives such as ***In vivo*** **Cellular and Molecular Imaging Centers (ICMICs)**, NCI has nurtured and promoted molecular imaging by supporting essential infrastructure and providing career stability to investigators in this emerging field of research. Each Center brings together experts such as biomedical engineers, cellular and molecular biologists, pharmacologists, and imaging scientists to conduct a program of multidisciplinary research on cellular and molecular imaging in cancer.

  One of the ICMICs has led the way in developing "smart contrast agents." When smart contrast agents are injected into the body, they are undetectable. However, when they come into contact with tumor-associated enzymes called proteases, the smart agents change shape and become fluorescent. The fluorescent signal can then be detected using sophisticated imaging devices. This first generation of smart agents are being further refined and developed by ICMIC investigators, and will have important applications in tumor detection and therapy assessment in the future.

  At the start of 2000, NCI established ICMICs at three sites around the country. The Institute has also awarded planning grants to 16 universities and research centers to begin to bring together investigators from a range of fields and initiate research projects in molecular imaging. NCI will select two of these to become full-fledged Centers by the end of 2001. In addition to their research activities, ICMICs will train new investigators and provide established investigators an opportunity to develop a multidisciplinary understanding of imaging, the basic science of cancer, and cancer care.

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[6] *Molecular imaging* techniques do not actually reveal molecules themselves, but detect signals that indicate the presence of biochemical activity and changes, such as cell growth or death. Thus, *molecular imaging* is often described as *functional*, because the processes being imaged are active and constantly changing.

- NCI is also helping to foster the development of new imaging contrast agents and molecular probes to improve the diagnosis and treatment of cancer through the **Development of Clinical Imaging Drugs and Enhancers (DCIDE)** program. In the first year of DCIDE, two agents were selected for further development: (1) a new contrast agent that enhances positron emission tomography (PET) imaging by targeting elevated levels of an enzyme present in prostate and other cancers and (2) a probe that can improve the accuracy with which magnetic resonance imaging (MRI) can reveal the earliest stages of the new blood vessel growth that accompanies a developing tumor.

- Animal models of cancers play an invaluable role in research, enabling scientists to investigate the development and progression of cancer; test new approaches to detection, diagnosis, and imaging; and evaluate prevention and treatment. With improved, genetically engineered mouse models for cancer becoming more widely available, investigators are able to use laboratory mice to study the development and spread of cancer and to test improvements in cancer imaging through the use of specialized equipment and techniques for imaging small animals. Since 1999, NCI has funded **Small Animal Imaging Resource Programs** at five research centers around the country to make the necessary equipment and personnel available to investigators and to improve and enhance technologies and techniques for imaging small animals.

  Investigators working with the Small Animal Imaging Resource Program at one university, for example, have been exploring the use of diffusion MRI (which measures the movement of water through and between cells) for imaging brain tumors. After validating their approach in small animals, imaging specialists have begun to test this new form of MRI in patients with brain tumors and other cancers. Initial results in patients, especially children, look very promising. If proven effective, diffusion MRI could dramatically reduce the time required to determine whether cancer patients are responding to therapy.

  Given the success of the Small Animal Imaging Resource Programs to date, NCI plans to initiate five additional programs in 2001. In addition, the Institute is actively working to foster broader use of these technologies. For example, NCI will co-sponsor a conference on the techniques of small animal imaging and has awarded supplemental funding to a number of scientists involved in the Mouse Models of Human Cancers Consortium to incorporate imaging research into their work.

- NCI, with the **National Science Foundation,** is cultivating further advances in the development of noninvasive imaging, monitoring, and therapeutic systems, with two projects focusing on the development of miniaturized optical probes. These probes, which provide very high-resolution images, are capable of detecting changes at the molecular level.

Bringing Advances in Imaging to Cancer Care

- As new cancer imaging technologies and techniques emerge and are refined, they often undergo further evaluation through one of NCI's clinical trials cooperative groups. These are networks of health care professionals affiliated with medical schools, teaching hospitals, and community-based cancer treatment centers. For example, NCI's newest cooperative group, the **American College of Radiology Imaging Network (ACRIN)**, is assessing the value of computed tomography scanning in screening patients for colon cancer, a technique sometimes known as "virtual colonoscopy." Because patient cooperation is critical to the success of any type of cancer screening, another group of NCI-funded investigators is also looking at patient preferences as one component of their comparisons of virtual colonoscopy and more traditional methods of colon cancer screening.

  ACRIN investigators are also evaluating the use of CT, MRI, and traditional tests for determining the spread of cervical cancer. To definitively answer questions about the value of digital mammography for breast cancer screening, ACRIN investigators have launched the largest study ever to compare conventional and digital mammography. They plan to compare the two methods in nearly 50,000 women over the next few years.

- At the same time, other NCI-sponsored networks are also evaluating the use of imaging technologies. Another cooperative group, the **American College of Surgeons Oncology Group**, is actively studying the use of PET scanning in patients with lung and esophageal cancer, to determine how far disease has advanced. In addition, the six study centers involved in NCI's ongoing **Prostate, Lung, Colon and Ovarian Cancer Screening Trial** are comparing the use of spiral CT with traditional chest x-rays in screening for lung cancer. A number of other investigators around the country are working to improve diagnostic imaging and image-guided therapy for prostate cancer.

  In addition to evaluating the use of various imaging technologies and screening and treatment procedures, NCI-supported scientists are using sophisticated imaging to assess the effects of new cancer drugs. For example, with many drugs that prevent the growth of new blood vessels, tumor shrinkage may not be readily apparent for some time. In cases such as these, functional imaging techniques can reveal whether the tumor is responding to therapy.

- Biomedical opportunities and scientific advances drive technology development in cancer imaging, but NCI recognizes that the regulatory environment in which this development takes place is critically important. To facilitate the transition of emerging cancer imaging technologies into medical practice, NCI created and coordinates a "sounding board" of Federal agency staff that advises investigators and manufacturers seeking to bring new imaging technologies to the marketplace. This group, the **Interagency Council on Biomedical Imaging in Oncology**, consists of staff from NCI, the Food and Drug Administration (FDA), and the Centers for Medicare & Medicaid Services (CMS –

formerly the Health Care Financing Administration). In confidential sessions three times a year, starting in June 2000, Council members provide advice to technology developers from academia and industry and discuss the evaluation of emerging technologies. Since September 1999, the NCI has also co-sponsored with industry an annual national conference on biomedical imaging in oncology that focuses on the research, regulatory, and reimbursement pathways of technology development.

Highlights of Recent Advances in Cancer Imaging [Box or sidebar]

High Powered Microscope Tracks Cell Changes. With funding from NCI, a multidisciplinary team of physicists, biologists, optical experts, and chemists has developed a new type of microscope combining the capabilities of nuclear magnetic resonance imaging with those of a traditional microscope. Using the combined microscope, investigators can examine how living cells react to changes in their environment, track the development of cancer, and study how cancer cells respond to treatment. In light of its potential significance for biomedical research, *Discover* Magazine with its 2001 Award for Technological Innovation in Health recognized the new microscope and the leader of the research team that developed it.

New Imaging Tools Provide More Accurate and Complete Diagnosis. Two groups of NCI-supported investigators working to improve cancer screening recently received Food and Drug Administration approval for computer-aided diagnosis systems to help radiologists assess the results of mammograms and chest x-rays. In these systems, computers are programmed to identify and highlight suspicious "hot spots" to ensure that all potentially cancerous points are examined.

Optical Biopsies an Option for the Future. NCI-funded scientists are developing imaging systems that may permit patients to undergo "optical biopsies" in the future and allow physicians to diagnose without the need for tissue samples. By modifying endoscopes and similar instruments to provide very high-resolution images for examining the gastrointestinal system, lungs, and other internal organs, investigators can now identify the cellular changes typical of early cancer when it is most treatable. In cases where these more powerful images can rule out cancer, such "optical biopsies" will allow patients to avoid unnecessary and painful tissue biopsies.

The Plan – Cancer Imaging

Goal

Accelerate discovery, development, validation, and clinical feasibility of imaging methods to identify the biological and molecular properties of precancerous or cancerous cells that will predict clinical course and response to interventions.

Objectives and Milestones for Fiscal Year 2003

1. **Expand the discovery, design, and development of novel imaging agents and devices.**

- Establish two additional *In Vivo* Cellular and Molecular Imaging Centers (ICMICs) to foster multidisciplinary research on cellular and molecular imaging in cancer.
- Establish a Network for Optical Technologies Development.
- Increase the number of imaging agents supported by the Development of Clinical Imaging Drugs and Enhancers Program from 6 to 12 per year.
- Use research supplements to increase collaborations between Small Animal Imaging Resource Programs (SAIRPs) and other NCI programs such as the Mouse Models of Human Cancers Consortium.
- Speed the development of specific imaging agents by funding grantees in a variety of NCI programs, such as ICMICs, SAIRPs, Interdisciplinary Research Teams for Molecular Target Assessment, Molecular Target Drug Discovery, and Molecular Target Laboratories.
- In collaboration with the developers, provide, for feasibility testing, innovative imaging device prototypes that have a limited market to academic institutions selected through a new competitive program.
- Support and add information to a publicly available database of imaging agents for the research community.
- Establish data banks of standardized digital image data associated with known clinical outcomes (such as virtual colonoscopy, digital mammography, digital chest imaging, and optical imaging for applications such as cervical, prostate, and oral cancers) to provide research resources for a variety of investigators.
- Fund six to eight grants to develop and test image processing and analysis algorithms using these standardized data sets.

2. **Integrate molecular and functional imaging methods into therapeutic clinical trials.**

- Increase the contract support for early clinical trials of imaging agents (safety and efficacy studies) from 8 to 12 trials per year.
- Provide expertise to clinical trials that use imaging by funding supplements for 10 to 15 imaging cores within NCI-funded Cancer Centers.

- Support expert panels to develop consensus criteria for using imaging results as endpoints in clinical trials.

3. Increase clinical trials of imaging methods and technologies.

- Expand a large randomized clinical study of spiral computed tomography as a screen in the detection of lung cancer, if initial data show a larger study is needed.
- Initiate clinical studies to: compare CT colonography (virtual colonoscopy) with endoscopic colonoscopy for early detection of colon cancer and polyps in a large multi-institutional setting; evaluate magnetic resonance spectroscopy for the early detection and assessment of prostate cancer; and evaluate the role of FDG-PET studies for monitoring tumor response to therapy.
- Support corollary imaging studies, such as monitoring response to therapy, with 10 funding supplements to Clinical Trials Cooperative Groups.

4. Accelerate the development and clinical testing of image-guided interventions.

- Use 6 to 10 funding supplements to enhance programs such as the SPOREs for image-guided therapy research that emphasizes a problem-solving, organ-specific approach and promotes interactions between clinicians and bioengineers.
- Increase collaborations between the Clinical Trials Cooperative Groups for testing promising, minimally invasive, image-guided interventions with four to six funding supplements.

Defining the Signatures of Cancer Cells: Detection, Diagnosis, and Therapy

The Opportunity

Every cell type, based on its functions, has unique, identifiable characteristics known as *molecular signatures*. These signatures may be active genes or proteins or other products manufactured by the cell. Today, with the aid of new technologies, scientists are working to read and understand these signatures and how they can be used for early detection, diagnosis, and treatment. They have learned that signatures change as normal cells become cancer cells and that these changes can be recognized as signals of the presence of cancer. Further, cells surrounding incipient tumors may also undergo changes, another indication that cancer is present.

Being able to read the signatures of easily accessed cells will help us to develop simple, non-invasive tests to find cancers located deep within the body. For example, tobacco-induced molecular changes in the mouth may predict lung cancer risk. Cancer cells that are "shed" in the urine may signal cancers of the urinary tract. In addition, identifying active and inactive genes or specific protein levels present in a particular tumor will provide us the opportunity to devise new ways to characterize tumors more efficiently. Such "molecular fingerprinting" will markedly improve the specificity of cancer diagnosis by allowing us to differentiate among tumors at the molecular level and enabling us to devise treatments targeted at cellular subtypes of different cancers.

By studying the sequence of changes that cells undergo as they are transformed from normal to cancerous, we will gain important insights into the etiology of cancer. For example, we can now use changes in molecular signatures to help us identify infectious and environmental agents that may be responsible for the development or progression of a tumor. In addition, while many of our previous efforts have centered on identifying genes involved in cancer, we are very interested in learning more about the cellular functions of the proteins produced by these genes. By assessing the meaning of individual changes in the cell's signature, we may be able to determine which cancers are most likely to progress and which are less likely to do so. This will be especially valuable to doctors and patients when confronted with hard decisions and the desire to avoid the consequences of unnecessary treatment. By reading cellular signatures accurately, we may be able to detect and diagnose cancers before they have a chance to invade nearby tissues. In fact, with the tools we are developing, a single drop of blood from a patient's finger may be all that is needed to find a cancer, assess the threat it poses by comparing its traits to profiles in an online library of tumor characteristics, choose the best possible treatment, and monitor a patient's recovery.

There has been a gap between the identification of preclinical tumor changes and the evaluation of new techniques that have the potential for clinical application. We now have the opportunity to synthesize these findings in signature research into a body of knowledge

that will translate into real health benefits. Our ultimate objective is to push back the detection and diagnosis of cancer to the earliest stages, thereby maximizing the potential to focus intervention efforts at preventing overt disease.

By identifying signatures, we can draw a valuable, though static, picture of the molecular composition of a cancer cell. This picture provides an opportunity to begin developing targeted diagnostics and therapeutics. To complete the effort, however, we will need a full understanding of the process of cancer initiation and propagation and how alterations in a few molecules might affect a variety of cellular functions. Specifically, we need to:

- Assemble the molecular signatures information into a complete picture of the living cancer cell.
- Confirm the diagnostic value of molecular-based methods.
- Confirm their practical benefits when compared to conventional medicine.
- Develop new technologies.
- Create and validate new pre-clinical models to establish our findings.
- Validate the predictive value of the new approaches by developing the sophisticated computer systems, databases, and statistical methods needed to integrate the complex information being generated by these new technologies with the relevant clinical data.

Progress in Pursuit of Our Goal

NCI is engaged in a number of activities to provide the resources needed to identify and categorize the molecular signatures of cancer. These resources include catalogs of molecular changes in cancer at the chromosomal and gene levels, materials ranging from genes to tissues, new technologies, and informatics tools that make these resources more accessible to the cancer research community. Taken together, these tools will assist researchers in their critical work to create new methods for detecting, diagnosing, and treating cancer.

Molecular and Analytic Resources Stimulate Research

NCI has expanded the development and availability of several molecular and analytic resources through genetic profiling and technology development.

- We are building the complete profile of expressed genes in normal, precancerous, and cancer cells through the **Cancer Genome Anatomy Project (CGAP)** (http://cgap.nci.nih.gov). This genetic profile will make it possible to recognize all major steps of tumor development, information that will guide future efforts to develop diagnostic indicators and identify targets for early detection or drug discovery. Researchers throughout the world have used CGAP data to identify potential molecular signatures of prostate, colon, ovary, breast, pancreas, and brain cancers and have documented their findings in scientific publications.

  CGAP consists of several initiatives. For example, the **Tumor Gene Index (TGI)** is the

most complete public catalog of gene expression for human cancers and for mouse models of cancer, containing more than five million gene-based DNA sequences. The goal for TGI is to build a complete index of cancer-related genes. Scientists will use TGI to classify tumors according to their molecular features to improve strategies for cancer prevention, early detection, diagnosis, and treatment.

The **Mammalian Gene Collection (MGC)** is extending the TGI to focus on identifying and cloning the full set of human and mouse genes to enable more rigorous study of individual genes, their protein products, and the role they play in human disease. Currently, potentially full gene sequences have been identified for about 15,000 human genes and 8,000 mouse genes.

The **Genetic Annotation Initiative (GAI)** has characterized and cataloged more than 25,000 human genetic polymorphisms important in cancer, providing scientists with insights about genetic variants associated with certain cancer types and those that may occur more frequently in some populations.

The **Cancer Chromosome Aberration Project (CCAP)** was established to generate a "Human Cancer Chromosome Aberration Map" using bacterial artificial chromosome (BAC) clones (selected for mapping studies because they contain large inserted segments of human DNA) as fluorescent probes to identify cancer chromosomal aberrations. In Fiscal Year 2001, CCAP passed a major milestone by producing an online version of the Mitelman Database of Chromosomal Aberrations in Cancer, a well-established and exhaustive reference of chromosome changes in human tumors. In Fiscal Year 2002, CCAP will complete a BAC fluorescence *in situ* hybridization map, linking the physical and cytogenetic maps of the human genome.

- The **Innovative Molecular Analysis Technologies Program (IMAT**) is supporting the development of new technologies to enable the discovery and use of molecular signatures of cancer. More than 100 research projects are under way, focusing on new approaches to analyze DNA, RNA, and proteins, as well as new methods to detect interactions of macromolecules in the cell. These approaches are designed to permit molecular classification of small numbers of cells, in support of the goals of detecting cancer at its earliest stage and understanding its origins.

- Through the **Unconventional Innovations Program,** NCI is supporting development of daring technological improvements in cancer treatment and detection in the 21st century. This program generates radically new technologies in cancer care to achieve the once impossible goal of detecting, diagnosing, and intervening in cancer at its earliest stages of development. It targets quantum improvements in existing technologies or entirely new approaches, rather than incremental ones, and actively stimulates the interest and involvement of investigators from disciplines not traditionally involved in NCI's technology challenges.

Tissue Resources Are Critical Resources for Signatures Research

Clinical specimens are a critical resource for the discovery and application of molecular signatures to cancer detection, diagnosis, and treatment. Responding to this need, NCI has established and made readily available to researchers a variety of tissue repositories.

- The **Cooperative Human Tissue Network (CHTN)**, **Cooperative Breast Cancer Tissue Resource**, and **Cooperative Prostate Cancer Tissue Resource** all provide researchers with easy access to high-quality tissue specimens. As the interest in reading the molecular signatures of cancer grows, so does the need for these resources. For example, the CHTN alone is now providing close to 50,000 samples per year. More than 1,000 investigators have been served by the CHTN, and about 200 new investigators request tissue each year.

- The **Shared Pathology Informatics Network**, a consortium of institutions connected by a model Web-based system, is working to improve scientists' access to human specimens along with relevant clinical data. The system will automatically access information from medical databases and respond to authorized queries by identifying, obtaining, and returning data for specimens that meet the defined search criteria, after removing any information that could compromise patient privacy.

- The **Tissue Array Research Program (TARP)** (http://cancer.gov/tarp) is responsible for the development of multi-tumor tissue screening microarray slides. The slides – which contain up to 600 tissue core samples from different tumor tissues as well as normal tissue and specific cell lines – allow for the high-throughput and comprehensive analysis of the molecular profile of each specific tumor type by enabling scientists to examine DNA, RNA, and proteins. They also can be used to further characterize molecules as potential molecular targets unique to each tumor tissue. Currently, TARP plans to further scale up production of these slides and is establishing a knowledge transfer and training program to disseminate the development of this technology to interested scientific investigators. TARP is also developing technologies to automate slide construction as well as data gathering, storage, mining, and analysis. TARP is the result of a collaboration among scientists at NCI and the National Human Genome Research Institute. Strategic planning and initial implementation for TARP, including the construction of the prototype microarray slides, took place during most of Fiscal Year 2000 at NCI's **Advanced Technology Center (ATC)**. During early Fiscal Year 2001, the ATC increased production capacity and distribution of quality-controlled slides, and these tools have been used extensively by the scientific research community

Molecular Signatures Are Useful for Studying and Validating Animal Models of Human Cancer

Models that truly reflect the behavior of human cancer promise to profoundly improve our ability to identify and understand the molecular changes associated with cancer's development and progression, and enhance our ability to evaluate a range of biomarkers prior to clinical use. NCI launched the **Mouse Models of Human Cancers Consortium** to develop and make available to researchers validated mouse models that mimic human cancers. See page x for a description of this program.

Molecular Signatures Lead to New Approaches for Early Detection

To support new approaches for early detection of cancer and determine biomarkers of precancerous lesions, NCI established the **Early Detection Research Network (EDRN)** in 1999 as a national research program focused on the discovery and development of novel markers for all cancers. EDRN scientists work to further refine molecular signatures of cancer (the signposts of a cell's progression toward cancer) and to harness their uniqueness. Through these efforts, signatures become molecular tools or "biomarkers" that can be used for cancer screening and detection. The design of the EDRN network (separate, yet coordinated development, validation, and clinical laboratories) helps to streamline the process of developing and evaluating promising biomarkers and technologies. In addition, EDRN encourages its participating laboratories to focus their research on highly prevalent cancers. This comprehensive, collaborative approach merges genetic pursuits with protein approaches, providing a systematic view of how the molecular signatures of specific cancers can be used as unique, identifying marks.

EDRN researchers are making progress in identifying biomarkers for the early detection of several types of cancer. In breast cancer studies, network researchers are characterizing proteins present in nipple aspirate fluid (NAF) in an effort to develop a noninvasive detection test for breast cancer. NAF, a substance that circulates in the breast ducts, is easily extractable and may provide a "snapshot" of the breast environment since proteins associated with the biology of the breast are secreted into this fluid. Using a protein chip-based approach and incorporating detection with mass spectrometry, investigators have demonstrated that different proteins can be identified in NAF samples from a cancerous breast compared with a normal breast in the same woman. Further studies are in progress to determine the validity of this approach with a large number of specimens. Investigators are exploring new approaches to detect esophageal cancer at its earliest stages, when the disease is most amenable to intervention. Preliminary EDRN data suggest that gene microarrays may be able to detect premalignant and malignant esophageal lesions with a high degree of accuracy. Pending validation with the larger sample size, these expression profiles offer the potential of subclassifying esophageal lesions by their strong tendency to progress and by their response to chemoprevention. Researchers are using protein chips to improve the sensitivity and specificity in detecting prostate cancer. Through this research, they have observed that serum PSMA is superior to PSA, the marker currently used for prostate cancer

screening, in distinguishing benign prostate hyperplasia from prostate cancer.

Better Classification of Tumors Improves Diagnostic Tests

The traditional molecular classification schemes for human tumors are based on tumor structure, but structure alone does not always accurately predict a tumor's biological behavior, treatment response, or prognosis. NCI is working to develop a more clinically predictive and useful classification system for diagnosing cancer.

- Through the **Director's Challenge: Toward a Molecular Classification of Tumors** initiative, investigators are developing profiles of molecular alterations in human tumors using DNA, RNA, or protein-based comprehensive analysis technologies. These molecular signatures will redefine tumor classification, moving from structure and form to molecular-based classification schemes. They also will provide more informative classification schemes for human cancers by identifying clinically important tumor subsets within morphological classes.

  Director's Challenge teams are working to identify molecular signatures for many types of cancer, including breast, prostate, lung, brain, ovary, hematopoietic, colon, Wilms, and sarcomas. One of these teams has developed molecular profiles that identify subsets of node- negative breast cancer patients. Tumors in one subset appear to arise from luminal cells in breast glands, whereas tumors in a second subset appear to arise from basal cells. Patients with basal cell tumors appear to have a significantly poorer outcome and may present node- negative breast cancer patients with a greater risk for recurrence. Studies are now under way to confirm and extend these initial findings.

- The **Program for the Assessment of Clinical Cancer Tests** (PACCT) facilitates the translation of new knowledge about cancer and new technologies to clinical practice. Activities include the generation of reference sets of clinical specimens, which will be made available to academic and industry researchers working to evaluate new markers and validate the utility of some known markers and tests. This program also is supporting the development of criteria to help determine the data needed to move a marker test forward to clinical practice.

The Plan – Defining the Signatures of Cancer Cells: Detection, Diagnosis, and Therapy

Goal

Generate a complete catalog of the distinguishing molecular signatures of normal, precancerous, and cancer cells at all stages in all tissues, and use the catalog to develop diagnostic techniques for the earliest detection of precancerous lesions and cancers; develop signature-based therapies; and identify subsets of patients with different prognoses to predict therapeutic response.

Objectives and Milestones for Fiscal Year 2003

1. **Expand the development and availability of molecular and analytic resources.**

- Initiate the Cancer Molecular Analysis Project to integrate molecular signatures, targets, and interventions.
- Complete the Mammalian Gene Collection for full-length human and mouse cDNAs.
- Continue to develop technologies relevant to discovering and measuring molecular signatures of cancer and precancer and the dissemination of technologies to the scientific community
- Continue to develop biosensors for detecting human cancer and cancer development through the Unconventional Innovation Program.
- Extend the Genetic Annotation Initiative to identify new gene variants relevant to cancer in clinically and epidemiologically defined populations, define key molecular pathways by characterizing comprehensive genetic variations on an extended set of gene and protein expression profiles, and develop time and tissue-specific human gene expression profiles from samples with measured exposures to facilitate the identification of epigenetic targets and further define mechanistic pathways of tumorigenesis.

2. **Establish and make available to researchers tissue resources to maximize the practical application of molecular signatures to problems in cancer research.**

- Establish a national tissue resource system for all major cancers, including cancers of the lung, breast, prostate, colon, head and neck, brain, soft tissue, blood, bone, the gynecologic and genitourinary systems, and childhood malignancies.
- Expand tissue repositories of precancerous lesions in all major cancers.
- Use Phased Innovation Awards to develop tissue preservation and sample preparation methods to increase their utility and compatibility with new technologies for cancer and precancer.
- Enhance the Web-based system to query pathology information systems, including pathology standardization and agreement on common data

elements.

3. Identify molecular signatures and apply them to the study and validation of animal models for human cancer.

- Continue to develop preclinical mouse models, and fund systematic analysis and phenotyping to validate them. Use these models to validate new molecular-based approaches for early detection, diagnosis, treatment, and prognosis of human cancer.

4. Support new approaches for early detection of cancer and to determine biomarkers of precancerous lesions.

- Establish easily accessible surrogate sites for more cost-effective, earlier cancer detection and risk assessment.
- Study molecular signatures to discover causative factors for cancer, including infectious and environmental agents.
- Identify and validate biomarkers to develop more sensitive and specific tools for early cancer detection and to assess their predictive accuracy for cancer occurrence.
- Develop a program based upon the use of low molecular weight protein patterns in serum for early diagnosis of prostate, breast and ovarian cancer. Expand marker identification program to predict disease stage and risk of recurrence.
- Expand studies to identify and validate epigenetic markers of cancer.
- Develop applied algorithms and statistical methods to analyze multiple biomarkers or a pattern of molecular changes and link those changes with clinical outcomes.
- Develop analytical prediction tools for risk assessment, incorporating molecular, genetic, and family history information.
- Implement, within the Early Detection Research Network, a Network-Wide Knowledge and Informatics Center.

5. Validate molecular classification schemes of cancer, and develop new diagnostic tests.

- Fund expanded validation programs for each major cancer site as results emerge from the Director's Challenge and other programs.
- Validate new diagnostic approaches through the Program for Assessment of Clinical Cancer Tests to provide the research community with a means to evaluate and validate signatures with possible diagnostic value.

6. Support basic research aimed at characterizing aberrant molecular interactions in cancer.

- Generate a comprehensive map of all cellular signal transduction pathways and their links to one another through a Signal Transduction Annotation Consortium.

- Support basic research efforts for analysis of: higher order cellular architecture that may be disrupted in cancer; organization of chromosomes into chromatin and their localization within the nucleus; and structure and function of molecular machines; and structure and function of membranes.
- Develop technologies for analyzing cell-cell interactions and communication that might be disrupted in cancer by funding 10 Phased Innovation Awards.

Molecular Targets of Prevention and Treatment

The Opportunity

We are entering a new era in cancer drug discovery. The convergence of advances in cancer biology, synthetic and biosynthetic chemistry, high-throughput screening, and medical imaging presents us with an unprecedented opportunity to develop a whole new generation of cancer prevention and treatment drugs that target the molecular features of cancer. By selectively targeting cancer cells, these revolutionary new agents promise to be less toxic and more effective than current drugs.

Our ability to understand cancer, or any other disease for that matter, has always been tied to available research technologies. The microscope, for example, could reveal whether a cell was cancerous, but nothing about what makes a cell cancerous or how its inner workings might differ from normal cells. Scientists working to discover effective prevention and treatment agents have for years faced the formidable barrier of not really knowing precisely what cancer is. As a result, techniques for identifying drugs to prevent or treat cancer have been limited to studying whether the drug would inhibit cancer development in animals or test tubes. Despite these limitations, scientists have identified through the years several synthetic and natural substances that appear to thwart cancer development, and we now have some drugs that, alone or with surgery or radiation, can cure some human cancers and ease symptoms in others.

However, most of the common tumors of adults do not respond well to currently available treatments. And even when treatments successfully shrink tumors or eliminate them from the body, they often harm the patient's quality of life with a variety of sometimes devastating short- or long-term side effects. Many of the most severe toxic effects of chemotherapy drugs stem from their non-selective nature. They kill or inhibit the growth not only of tumor cells, but of a number of healthy cells as well. With current technology, we want to develop more selective drugs that target the molecular differences between tumor and normal cells. These new drugs should be much more selective, more effectively targeting the cancer but without the associated side effects.

The situation for prevention is similar. Knowledge of the precise molecular steps that characterize premalignant change will allow us to find agents that reverse these changes or at least block their further development into cancer.

At this point in time, we have been able to identify numerous potential molecular targets as an early step in cancer prevention and treatment drug discovery. To continue to move ahead, we need to create better ties among the key components of the discovery-development-clinical testing process. We need to pursue questions about a new drug's effect on malignant or precancerous cells: Does the drug kill the cancer or effectively block its growth and spread? What part of the cell's complex machinery does it disrupt, and is this disruption

related to its anti-cancer effect? Tools to address the second question have been crude and inadequate, so our clinical testing has focused only on the first.

We must gather the knowledge and develop the tools to answer the latter question. When we can, we will be ready to tackle questions that can lead to improved cancer treatment. If a drug is working well, why is it working? If not, why not? Are we giving patients the right amounts, too much, or too little? Must we give people the maximum dosage they can tolerate, or can we judge the right amount by whether the drug is getting to the tumor and affecting its target? Will the drug harm the patient now or in the future? Only when we can answer these questions will we be able to predict who is likely to respond to a particular treatment and who will not. Laboratory and clinical studies, working together, will provide the basis for designing even better drugs in the future.

Progress in Pursuit of Our Goal

Our ever-increasing knowledge of the molecular changes that cause a normal cell to become a cancer cell has paved the way to a whole new approach to cancer drug discovery. Researchers are developing a new generation of cancer drugs that target these molecular changes to delay, stop, or reverse cancer growth. This development of "smart" drugs involves a multi-step process that begins with the search for molecular targets in the cancer cells. A molecular target might be a cellular process or pathway that is no longer regulated by the cell, allowing cancer to develop. Scientists then validate these targets to determine whether they might be able to find a drug that will interact with, or "hit," the molecular target to prevent or treat the cancer. Next they generate and test the function of a repertoire of potential anti-cancer agents against these targets, and finally they take the steps needed to test candidate drugs in the clinic. NCI is advancing this new approach to drug discovery through a number of initiatives, many of which are described below.

Identifying and Validating New Targets for Drug Discovery

Through the **Molecular Target Drug Discovery (MTDD)** program, investigators are identifying novel molecular targets, validating these targets as sites that can be exploited for cancer therapy, and developing tests that determine how well potential agents work on these targets. The 41 groups currently supported through this program are studying a number of different molecular targets. For example, one group of scientists is investigating the Bcl-xL protein, an aberrant protein that enables cancer cells to evade apoptosis.[7] Another group is studying the cellular "stress response" protein, Heat Shock Protein (HSP) 90, which is overexpressed in tumors and may play an important role in cancer growth. And, a group is evaluating the role of altered DNA methylation, particularly in tumor suppressor and DNA repair genes. Changes in DNA methylation can cause tumor development by silencing genes that normally control cell growth.

[7] Apoptosis is the body's quality assurance system, which directs damaged and abnormal cells to destroy themselves.

NCI and the National Institute for General Medical Sciences are working together through the **National Beam Program** to construct the x-ray beamline at the Argonne National Laboratories in Fiscal Year 2002. This cutting-edge technology will greatly improve scientists' ability to determine the 3-dimensional structure of proteins and larger multi-molecular complexes. This key technology allows scientists to quickly identify the structure of important molecular targets in cancer cells and to use efficient computer modeling to identify potential anti-cancer agents that will be effective against the individual targets based on their structure.

Exploiting Targets for Drug Discovery

The **Molecular Targets Laboratories (MTLs),** first funded in FY 2002, will capitalize on the opportunities emerging from advances in genomics, molecular biology, combinatorial chemistry, informatics, and imaging. Through this initiative, scientists apply advances from these diverse areas to create a resource of biological assays and chemical probes for cancer-related targets. This work enables biological studies of cancer, including physiological and biochemical monitoring, and provides a platform for drug discovery.

Through the **Mouse Models of Human Cancers Consortium,** groups of academic researchers have created and are making available to the public mice with defined genetic alterations that predispose the animals to certain types of cancer. Six strains are currently available, and up to 30 more may be added annually. These animals could serve as a basis for testing new treatment and prevention strategies that target the molecular abnormalities giving rise to the cancers. As more animals are added to NCI's collection, it will be possible to create subsequent generations of mice with more than one genetically defined alteration, even more closely resembling human tumors. Academic members of the consortium are also developing ties to pharmaceutical industry sponsors to facilitate the testing and evaluation of new compounds in these mouse strains. For more information about this initiative, see page x.

Finding Compounds That Hit the Targets

Through several NCI initiatives, chemists and biologists are working collaboratively to create libraries of synthetic, biological, and natural compounds that will be tested for therapeutic potential against molecular targets. These scientists are developing "smart" assays, or tests used to screen the compounds to identify those that "hit" defined target molecules.

- One of these initiatives, the **National Cooperative Drug Discovery Groups** program, supports innovative, multidisciplinary, multi-project approaches to discovering new rationally synthesized or naturally derived anticancer treatments.

  Thirteen funded groups are progressing in a variety of areas, including an innovative

effort to design and evaluate novel anti-cancer drugs that inhibit the enzyme geranylgeranyltransferase I (GGTase I). This enzyme is involved in activating the complex *Ras* signaling pathway, which has been implicated in a number of human cancers. Researchers hope to identify an agent that will selectively suppress GGTase, in turn suppressing the cancer-promoting activity of the *Ras* pathway. This research is an excellent example of how a basic discovery generated through an R01 grant can be expanded into clinical development with support from special NCI initiatives.

- In **Biology-Chemistry Centers**, multidisciplinary teams of scientists use a combination of chemical and biological techniques to create libraries of chemically diverse structures with potential anti-cancer effects. Using "smart" assays, scientists screen the compounds to identify those that specifically interact with cancer-specific molecular targets. The six teams funded through this initiative have screened hundreds of thousands of compounds for anti-cancer activity.

  Promising compounds include the newly designed GFB-111 molecule. This novel molecule binds to growth factors – normal proteins that help to promote new tissue growth - and has been shown to significantly inhibit blood vessel formation (angiogenesis), and thereby growth, in human tumors grown in mice. Its success represents the potential for designing molecules with potent antiangiogenic activity.

- NCI supports **the collection of natural extracts** from plants throughout the world. Using high-throughput screening tests, scientists evaluate the potential for using these extracts either as probes to more fully define targets or as anti-cancer agents aimed at new cancer targets. For example, Halichondrin B, a naturally occurring chemical found in a Pacific Ocean sponge, has been found to have considerable anti-tumor activity. This chemical can irreversibly block cell division because it targets and binds to tubulin, a protein important to cell division. Because the scarcity of halichondrin B has limited its potential as an anti-cancer agent, researchers started designing structurally simplified, synthetic analogs. Two promising analogs have shown significant anti-tumor activity against human breast, colon, melanoma, and ovarian tumors grown in laboratory animals and will next be studied for clinical usefulness.

- The **Rapid Access to NCI Discovery Resources** (R*A*N*D) is a new program that expedites the development of drug research capabilities in academic institutions. R*A*N*D focuses on laboratory-based studies that are the starting points for new drug development, supporting early formulation, pharmacokinetic, pharmacology, and toxicology studies. R*A*N*D assists in the development of high-throughput laboratory assays to screen large numbers of chemicals shown to have initial promise. The program supports the development of "libraries" of chemicals that scientists can draw upon for study. Chemical libraries contain *lead structures* – chemicals believed to have potential as molecular target drugs – as well as chemicals that have promisingly similar structures. One of the five initial R*A*N*D projects involves use of micorarray technology to study molecular profiles of leukemia cells and identify more targets. Another exciting project involves creation of a library based on a compound that targets an important cellular

protein involved in the development of blood supply to tumors, without which they cannot grow.

- **Resources of synthetic chemicals, collected natural products, and biological materials** are available at no cost for samples to cancer investigators who want to screen them as molecular targets. NCI has made available more than 140,000 synthetic chemicals, 80,000 natural products extracted from plants and marine organisms, and a variety of biological agents (monoclonal antibodies, cytokines and reference agents).

Turning a Promising Target-Directed Compound into a Drug for Human Use

Translating a laboratory discovery into an agent for human use is an exacting task that requires very specific, interrelated activities. For example, sufficient quantities of the drug must be made for formulation, stability, and safety testing. Drug optimization and development studies enable scientists to determine the manner and amount of drug to be delivered based on a drug's overall effect on an animal. NCI is supporting this critical arm of drug development through a variety of initiatives.

- The **Rapid Access to Intervention Development** (RAID) program provides preclinical drug development resources to academic institutions. The 50 current projects support early-preclinical studies, late preclinical studies, or full development of promising agents.

  Two interventions developed through the RAID program are now being tested in clinical trials. One intervention is a novel gene therapy approach that involves delivering a pair of therapeutic "suicide genes" to prostate tumors, thereby rendering malignant cells sensitive to specific drugs and radiation. The other is the anti-cancer agent 6-Diazo-5-Oxo-l-Norleucine (DON), which selectively inhibits growth of neuroendocrine tumor cells. As many as nine additional agents will be in clinical trials testing by the end of Fiscal Year 2001.

- **The Rapid Access to Preventive Intervention Development** (RAPID) program provides preclinical and early clinical drug development resources to academic investigators working to develop novel agents directed at preventing, reversing, or delaying cancer's development. The seven projects currently funded through RAPID include studies developing certain marine-derived products as chemopreventive agents, a human papillomavirus vaccine, and work to determine the preventive effects of certain proteins from rodent embryonic tissue.

- **The Drug Development Group** provides support for academic and corporate-derived compounds when NCI is responsible for conducting and monitoring the drug's clinical development. A number of promising agents have been developed through this program.

  PS-341, a novel compound presented to NCI by Millennium Pharmaceuticals, is the first

in a new class of agents that take aim at a new cellular target - the proteasome enzymes. These enzymes play an important role in the breakdown of proteins that regulate the cell cycle. PS-341 inhibits the breakdown of these proteins and induces cell suicide. In Phase 1 clinical trials, PS-341 produced promising effects in both multiple myeloma and prostate cancer patients. NCI and Millenium are now pursuing further clinical testing.

Certain oncogenes[8] block the normal expression of other genes in healthy cells. Histone deacetylase (HCAC) inhibitors relieve this suppression. In cooperation with extramural organizations, NCI has studied the anti-tumor effects of several compounds in this class of drugs, including pyroxamide, an HDAC inhibitor presented to NCI by Memorial Sloan-Kettering Cancer Center as a candidate for cancer drug development. Pyroxamide considerably reduced tumor growth in animal models of breast, lung, and prostate cancer without causing toxicity. Phase I clinical trials are now under way at Memorial Sloan Kettering. MS-275, from Mitsui Pharmaceuticals, is being developed jointly in the United States through a Cooperative Agreement with NCI.

- The **Flexible System to Advance Innovative Research** (FLAIR) provides small businesses the budget resources required to develop cancer therapeutic and prevention agents from basic discovery to proof-of-principle in clinical trials. There are currently 20 active FLAIR grants, including an investigation of a potential anti-cancer agent, PX-12. This agent targets thioredoxin, a cellular protein that is overexpressed in a number of human cancers and is associated with aggressive tumor growth and poor patient prognosis. PX-12, which inhibits the growth-promoting activities of thioredoxin, has shown potent anti-tumor activity against leukemia, breast, and lung cancers in animal models. Phase 1 clinical trials supported by the FLAIR program are now under way.

Developing Clinical Trials Programs To Study New Molecularly Targeted Agents

The **Interdisciplinary Research Teams for Molecular Target Assessment** (IRTMTA) is a new program that enables interdisciplinary teams of scientists to develop methods (molecular assays, molecular and cellular imaging probes, and other tools) to assess the effects of specific targeted interventions in preclinical models and in proof-of-principle early clinical trials. Each team will focus on a critical biological process thought to contain high-priority targets for cancer prevention or treatment drug discovery. The first set of applications for this program was funded in early FY 2001.

[8] Cancer-causing genes

The Plan – Molecular Targets of Prevention and Treatment

Goal

Facilitate the expanded exploration of the causes of cancer and the discovery and development of agents that specifically "target" these causes to treat and prevent cancer.

Objectives and Milestones for Fiscal Year 2003

1. **Identify, characterize, and validate the combinations of deregulated cellular proteins and pathways that cause cancer in precancerous and cancerous cells.**

- Through the Molecular Target Drug Discovery Grants (MTDD), increase support for researchers working to identify and use cellular targets for the discovery of new anti-cancer agents. Continue support for the MTDD Grants and previously awarded Biology-Chemistry P01s. Provide screening assistance and informatics management.

2. **Determine the cancer-causing deregulated pathways that can be targeted by prevention or treatment agents.**

- Amplify support for the Molecular Target Laboratories for the development of assays to identify possible treatments for cancer and for the acquisition of large libraries of natural and synthetic compounds; both will be critical in the systematic search for new preventive and therapeutic agents.
- Support the Mouse Models of Human Cancers Consortium to accelerate the pace at which accurate, reproducible mouse models of human cancers are made available to the research community for further investigation or application.

3. **Provide the infrastructure for researchers to develop assays to test large numbers of potential drugs against validated "drugable" deregulated proteins and pathways**.

- Expand support for the National Cooperative Drug Discovery Groups.
- Expand the reach of NCI discovery resources to academic laboratories through the Rapid Access to NCI Discovery Resources (R*A*N*D) program.
- Expand efforts to collect, inventory, and distribute diverse materials from all sources - synthetic chemicals, collected natural products, and biological materials, and provide informatics support that can be made available for anti-cancer research.
- Develop a translational research program that will closely link molecular imaging, cancer signatures and molecular targets. This

would allow serial imaging, with conventional and innovative technology and serial biopsies to assess genomics and proteomics to be coupled with therapeutic intervention using systemic agents, radiation therapy, immunologic treatment and chemopreventive agents. The ability to conduct multiple studies will provide a robust data set by which to understand the biology behind the image to credential new molecular targets.

- Support an intramural Molecular Targets Drug Discovery Program that will develop screening assays for biomolecules that interact with molecular targets, conduct initial screens for bioprobes and inhibitors of molecular targets, characterize and validate hits from these screens, and facilitate development of new research reagents and clinical lead compounds. Support the isolation, purification and physico-chemical characterization of active materials and compounds contained in natural products extracts.
- Develop a clinical proteomics initiative utilizing laser capture microdissection of human tissue specimens along with developing new protein array, 2D-PAGE, signal pathway profiling and SELDI-TOF protein pattern fingerprinting for clinical proteomic applications in human cancer and drug toxicity detection.

4. Facilitate the steps necessary to turn a target-specific lead compound into a clinical agent.

- Expand support for the highly successful Rapid Access to Intervention Development (RAID) program.
- Increase funding to the Rapid Access to Preventive Intervention Development (RAPID) program to support the development of prevention agents from the laboratory to the clinic for clinical trials of efficacy.
- Expand our assistance to small businesses through the Flexible System to Advance Innovative Research (FLAIR) program.

5. Fund Clinical Trials Networks that will take drug candidates into human trials designed to test whether or not the drug is working against the intended target and is affecting the progression of the cancer in the intended manner.

- Continue and widen support for the Interdisciplinary Research Teams for Molecular Target Assessment (IRTMTA) program.

Research on Tobacco and Tobacco-Related Cancers

The Opportunity

The devastating impact of tobacco use and tobacco smoke exposure on the incidence of cancer, heart disease, and stroke is both compelling and conclusive. Tobacco use causes more premature death than that caused by all drugs of abuse combined, and lung cancer would be a rare disease in the absence of smoking.

A unique challenge in the fight against tobacco-related cancers is that addiction to nicotine, a key substance in tobacco, drives the continued use of tobacco even when the user is fully aware of increased risk of disease and premature death. Some people will continue to smoke even as they undergo treatment for a life-threatening disease. Furthermore, tobacco-related diseases such as lung cancer remain some of the most difficult to treat effectively.

We need to better understand the genetic, biological, behavioral, and social influences that explain:

- Why children and adults use tobacco
- How they become addicted
- Why those who become addicted have such difficulty quitting
- How to prevent, detect, and treat cancers caused by exposure to tobacco and its constituents

NCI's commitment to preventing, diagnosing, and treating tobacco-related cancers began more than 40 years ago and remains one of our highest priorities. Our research has benefited individuals and has improved the public's health. Yet, we continue to pursue new questions as we learn more about the complex challenges of tobacco use and tobacco-related cancers.

Progress in Pursuit of Our Goal

NCI has a unique role in supporting the entire range of tobacco research, from understanding why and how people use tobacco to developing more effective treatments for nicotine addiction. We also focus on detection and treatment of tobacco-related cancers and metastatic disease. NCI has a special concern for the health of former smokers, people who followed advice to quit smoking, who comprise about half of those diagnosed with lung cancer. The breadth of NCI's support is reflected in our investments both in basic biological research on the effects of tobacco exposures and in community-based studies of smoking prevention programs.

Recent advances in knowledge about tobacco use and tobacco-related cancers provide an unprecedented opportunity to reduce the disease burden from tobacco. New evidence is helping to better explain why some people are more vulnerable than others to DNA damage

caused by tobacco exposure. Research on the early detection of lung cancer suggests that it may soon be possible to identify cancers in smokers at a much earlier and more treatable stage. Recent studies of teen smokers have identified psychological factors that increase the risk of becoming addicted, as well as the need to provide younger smokers with specialized programs to help them quit. A new evidence-based guideline enables healthcare providers to offer smokers effective strategies to quit smoking. If applied widely, this could have a dramatic effect on the number of smokers who successfully quit. Also, new cancer treatments based on molecular targeting provide models for how to increase the effectiveness of therapies for tobacco-related cancers.

NCI has a number of research initiatives under way to inform our understanding of tobacco use and tobacco-related cancers. Following are examples of major activities related to the objectives of the Research on Tobacco and Tobacco-Related Cancers Opportunity.

Preventing, Treating, and Screening for Tobacco-Related Cancers

Lung cancer studies are the focus of much of our research on tobacco-related cancers. Many of the lessons from lung cancer may be applicable to other cancers as well.

- A chemoprevention and biomarker study involving lung cancer survivors and patients at high risk for lung cancer is under way**.** Chemoprevention strategies include the use of drugs, vitamins, or other agents to reduce the risk or delay the development or recurrence of cancer. The **Lung Cancer Biomarkers and Chemoprevention Consortium** began recruiting patients in the summer of 2001 to participate in two trials evaluating chemopreventive drugs. Researchers will perform biomarker analyses on tissues obtained during the studies and correlate these findings with patient outcomes. Three of NCI's Specialized Programs of Research Excellence (SPOREs) in lung cancer and other non-SPORE institutions are participating in these trials.

- The **Lung Cancer Screening Study** began in 2000 to assess the feasibility of the spiral computed tomography (CT or CAT) scan to detect early lung cancers. Although spiral CT scans are advertised as a new way to find early lung cancer in both current and former smokers, questions remain unanswered regarding the technology's risk and benefits. Detecting these early tumors has not yet been proven to reduce the likelihood of dying from lung cancer, the gold standard for any screening test. Moreover, there is concern that the spiral CT scan may pick up non-cancerous changes in the lung and trigger patient concern, unnecessary invasive testing, or even chest surgery.

  As of the spring of 2001, 3,000 people were randomized to either a spiral CT or a chest X-ray. Over the next two years, NCI will expand this study to include 15,000 people. Similarly, ongoing studies as part of the NCI-supported **Prostate, Lung, Colorectal and Ovarian screening trial** are examining whether annual chest X-rays, which are easier to perform than the spiral CT scans, can reduce mortality from lung cancer.

- Through two new initiatives begun in the summer of 2001, NCI will fund **preclinical and clinical studies to identify newer, more potent agents that may prevent cancers in former smokers**. Using animal models that mimic the conditions of former smokers, researchers will identify and validate biomarkers for tobacco-related cancers in these models. Organ systems of interest to the researchers include the lung, head and neck, bladder, esophagus, pancreas, cervix, and colon. In a second related initiative, NCI will fund pilot clinical trials to evaluate the efficacy of chemopreventive agents in a group of former smokers. These studies will evaluate molecular and imaging endpoints to examine the effects of these new agents in this group of people at increased risk for developing invasive cancers. Currently, almost half of all new cases of lung and bladder cancer occur in former smokers. It is vitally important to the public's health to identify molecular and imaging markers of cancer risk and early neoplasia (abnormal and uncontrolled cell growth) and to test agents that can prevent the development of cancer in this group.

Understanding the Interplay Among Tobacco, Other Exposures, and Cancer

While costly and resource-intensive over long periods of time, cohort studies that include genetic and biomarker components have been recognized as invaluable tools for collecting large amounts of information critical to understanding cancer risk. Through these prospective studies, cancer-causing exposures can be assessed before cancer diagnosis, and multiple cancer endpoints can be studied. A few examples illustrate the value of these studies to research on tobacco-related cancers.

- The **Prostate, Lung, Colorectal, and Ovarian screening trial** is examining emphysema in relation to smoking, how genetic factors influence smoking, and the differences between current and former smokers regarding genes that might be involved in nicotine dependency. This resource will prove increasingly precious over time as cancer cases develop in the cohort and their biospecimens become available for special study.

- Through an NCI-supported **study of a cohort of women in Shanghai,** we have an unprecedented opportunity to prospectively collect data and biospecimens from both non-smoking women who are exposed to second-hand smoke in their homes and their husbands who tend to be active smokers. Blood and urine samples from these women and men will provide unique research opportunities. Similarly, we have incorporated major biospecimen collections into studies that compare groups of people with cancer to healthy control groups. Specific studies initiated during the past year focused on smoking-related cancers such as lung, bladder, and renal cancers.

- NCI supports **regional biorepositories, such as the expanded Frederick Biorepository and the Cooperative Human Tissue Network**, which fill a critical need by housing and maintaining human biospecimens such as tissue, blood, and urine. Scientists collect these biospecimens from large-scale studies, such as those described above, and make them

available to researchers.

Understanding and Preventing Youth Tobacco Use

The need to develop more effective strategies to prevent teenage smoking and help young smokers quit presents a pressing research challenge. Tobacco use arises from a variety of influences, including social factors like peer and parental smoking, as well as biobehavioral and genetic factors. Because the majority of smokers begin using tobacco before the age of 18, understanding why youths use tobacco is a high priority for NCI.

We have substantially expanded our support for **studies that test ways to prevent tobacco use among the young and to help users quit**. NCI, in collaboration with other NIH institutes, is now supporting more than 50 research grants related to adolescent tobacco use prevention, dependence, and cessation. This wealth of cutting-edge research is beginning to yield new insights into youth tobacco use.

In June 2001, NCI brought together more than 200 investigators from across the country to share the latest scientific evidence concerning tobacco use among youth. **Research indicates that both social influences and inherited factors are predictors of youth tobacco use.**

- Results of a recent study of fifth- and eighth-grade students from New England middle schools showed that students who viewed more tobacco use in movies were more likely to have tried smoking than those who viewed fewer occurrences.

- Studies of twins show that inherited factors also influence whether a person will smoke and how difficult it will be to quit.

- To find the human genes associated with addiction, scientists are looking for clues within the brain's reward system. For example, the brain chemical dopamine has been shown to play an important role in people's craving for addictive drugs, including nicotine. Molecular genetic studies are underway to identify the specific genes responsible for these effects.

Results of **ongoing research supported through the Transdisciplinary Tobacco Use Research Centers are beginning to provide information on youth tobacco use**. NCI, the National Institute on Drug Abuse (NIDA), and the Robert Wood Johnson Foundation (RWJF) funded seven Transdisciplinary Tobacco Use Research Centers (TTURC) at U.S. academic institutions in 1999. Each Center is organized around a special theme, and researchers are tackling a wide range of studies that examine the relative influence of genetic and environmental factors on tobacco use. These Centers are making excellent progress, yielding significant results during the past year.

- Research has shown that smokers with a unique genetic makeup started smoking almost

two years earlier than smokers without this genotype. Investigations of genes important in smoking have focused on the dopamine system and on another brain chemical, called serotonin. Serotonin plays a role in depression and anxiety, both traits that have been associated with smoking behavior.

- Another study assessed factors that are associated with high school students' decisions to smoke. High academic performance, perceived academic competence, and involvement in school-related clubs and sports teams decreased the risk of smoking, while alcohol or marijuana use and novelty-seeking increased risk.

- A study at one TTURC examined factors that affect the progression of smoking initiation and use among youth of diverse cultures. Early results of this research suggest that the pattern of smoking initiation in the United States and China is similar, and that the optimal age for beginning smoking prevention interventions is between 10 and 15. This tells us that many of the programs aimed at youth start too late.

Treating Tobacco Dependence

Smoking cessation remains among the most cost-effective approaches to reducing cancer risk. However, despite the dramatic advances in understanding the nature of nicotine dependency during the past decade, the best treatments are effective for less than a third of all smokers who try to quit. NCI continues to support **new behavioral and pharmacological treatments as well as the application of effective treatment approaches** in the community.

- With NIDA, NCI created a working group to advise both Institutes on key areas where progress can be achieved in the development of new medications for smoking cessation. Understanding the genetic factors related to nicotine initiation and dependence will be critical to the development of new medications to help smokers quit.

- NCI supported innovative smoking cessation interventions that are tailored to the unique needs of individual smokers. For example, one recent study found that an "expert system" intervention, which provided computer-assisted feedback and help, resulted in quit rates that were almost 33 percent higher than a control condition. Because this study was conducted in a health care system, it opens the door for increased assistance to smokers in environments where maximum medical follow-up is possible.

- A recent study funded through the NCI Special Programs of Research Excellence (SPOREs) initiative (see p. xx) showed that those smokers who carried the DRD2-A1 genotype were more likely to relapse than those who carried the DRD2-A2 genotype, suggesting the possibility of developing tailored approaches to treatment that take into account unique genetic traits.

Smokers who do not wish to quit or who are unable to do so comprise a target market for the

tobacco and pharmaceutical industries. The tobacco industry is developing and marketing new products intended to reduce the harm of continued smoking, and the pharmaceutical industry is developing medications for smoking reduction, along with those for cessation. Nevertheless, there is little evidence to suggest that changing tobacco products or using medications for smoking reduction will result in decreased harm.

NCI collaborated with the Centers for Disease Control and Prevention (CDC), NIDA, RWJF, and the Legacy Foundation to hold a **Conference on Reducing Tobacco Harm** in May 2001. This conference brought to the forefront critical research questions such as:

- What is the dose-response impact of individual toxins that occur in tobacco smoke?
- What type of smokers will choose harm reduction products over quitting?
- Is there potential for such products to decrease the desire to quit smoking?

In order to remain at the leading edge of this important area of research, NCI will devote additional resources to address difficult issues, ranging from carcinogen delivery to the public health implications of using tobacco products and medications to reduce tobacco harm.

International Efforts

As NCI and its partners address tobacco control in the United States, it has become clear that our efforts can be informed by research conducted in other countries. Furthermore, tobacco products are being used in increasing quantities globally as the U.S. market changes. Research areas of particular importance are:

- Surveillance of the changing global patterns of use
- Development of scientific and public health networks that can optimally address tobacco control around the world
- Development of interventions for preventing and treating tobacco use

In support of global tobacco research efforts, NCI has:

- Partnered on a Global Youth Tobacco Survey led by the Centers for Disease Control and Prevention. The aim of this survey is to document and monitor the prevalence of and contributing factors to youth tobacco use.
- Contributed to the design and funding of a new research initiative led by the Fogarty International Center that will support international tobacco and health research as well as capacity-building efforts and studies that emphasize tobacco control research in low- and middle-income countries.
- Initiated a new lung cancer study in Milan, Italy, to evaluate gene-environment interactions in the development of lung cancer. This study includes the genetics of nicotine addiction and the treatment of smoking dependence.

Tobacco and Tobacco-Related Cancers: Good News and Bad

The Good News

- Comprehensive state/community tobacco control programs work. For example, Arizona's adult tobacco use dropped from 23.1 percent in 1996 to 18.3 percent in 1999.
- Smokers do want to quit. Approximately 39 percent of all adult smokers made an attempt to quit in the past year.
- Consumption of cigarettes continues to decline, dropping from 4,345 per capita in 1963 to 2,146 per capita in 1999.
- Lung and bronchus cancer deaths are estimated to drop from 158,700 in 1996 to 157,400 in 2001, primarily due to decreased smoking.

The Bad News

- Youth smoking increased from 28 percent in 1991 to 35 percent in 1999, with the highest percentage between ages 18-24.
- Those with the least education and income smoke the most: 11 percent of college graduates smoke, compared with 34 percent of those who did not finish high school.

- Lung cancer would seldom occur if people did not smoke – but it now kills approximately 157,000 people each year.

The Plan – Research on Tobacco and Tobacco-Related Cancers

Goal
Understand the causes of tobacco use, addiction, and tobacco-related cancers, and apply this knowledge to their prevention and treatment.

Objectives and Milestones for Fiscal Year 2003

1. **Expand efforts to define the biological, behavioral, and social bases of tobacco use and addiction.**

- Initiate prospective observational studies of the quitting and relapse process, including the effectiveness of medications.
- Improve understanding of the social bases of tobacco use by supporting studies of economic, geographic, sociocultural, and policy-related factors.
- Continue support for including questions on tobacco use in the Current Population Survey.
- Support analytical tools, resources, and analyses of existing and new tobacco use data.
- Expand collaborative efforts aimed at the translation of research findings on the determinants of tobacco use to clinical and community intervention research.

2. **Accelerate progress in understanding the interplay among tobacco, other exposures such as alcohol and asbestos, and host susceptibility on cancer risk.**

- Support clinical and population studies that include tissue and biospecimen resources to investigate the genetic, biological and behavioral factors influencing vulnerability to smoking dependence and tobacco-related cancer.
- Integrate biospecimen collection into screening trials to better understand the molecular basis of early-stage lung cancer.
- In collaboration with other Federal agencies, synthesize the latest evidence regarding environmental tobacco smoke and identify critical directions for new research.
- Support studies of the mechanisms of susceptibility to tobacco-related cancers to understand the effects of specific forms of tobacco and types of tobacco exposure.
- Integrate the use of mouse models into research on the development of tobacco-related cancers to identify the relative contributions among the genes related to susceptibility and resistance and other endogenous and exogenous factors.
- Facilitate scientific collaborations between lung and head and neck cancer SPORE investigators and TTURC investigators to better integrate biological, pharmacological, and behavioral research on tobacco use and its

impact on disease.

3. Develop, test, and disseminate more effective interventions to prevent and treat tobacco use and tobacco-related cancers, especially in high-risk individuals and groups.

- Support the development of biomarkers of tobacco exposure and risk through collaborative work with National Institutes of Health laboratories and those at the Centers for Disease Control and Prevention National Center for Environmental Health.
- Provide supplements to the Transdisciplinary Tobacco Use Research Centers, State/Community Tobacco grants, and Cancer Centers to stimulate health disparities research, including clinical assessment and care of tobacco-related cancers, differential tobacco use, and quitting patterns.
- Support collaboration with public and private tobacco research funding organizations to identify and disseminate successful tobacco use prevention interventions.
- Support the development of NCI's new tobacco treatment and research clinic to speed the discovery and testing of new treatments.
- Accelerate the identification of new treatments for nicotine addiction through the creation of an NCI/National Institute on Drug Abuse drug development and clinical trials collaborative.
- Support research on smoking cessation and relapse prevention in cancer patients and survivors.
- In order to accelerate the development of new, molecularly based treatments for lung cancer, support a molecular defects database, a tissue resource, and improved exposure assessments to enable more sophisticated studies of treatment outcomes.

Cancer Communications

The Opportunity

It is not unusual today for newly diagnosed cancer patients to go to their doctors' appointments armed with printouts from CancerNet or other Web sites and lots of questions. People have more ways than ever to get information: by telephone, fax, email, the World Wide Web, TV, radio, and in person. And the future holds even more choices: automated monitoring of vital signs, voice recognition software, wider use of wireless technology, and other technologic advances to make it easier and faster for people anywhere to get access to the best information about cancer.

NCI's opportunity is to optimize the use of these tools while enhancing the absolutely essential interaction of patients with their doctors and nurses. Indeed, new communication tools can facilitate partnerships between patients and their physicians. We must push forward the frontiers of technology in support of the public, patients, their families, and medical teams to ensure access to individualized, high quality, NCI-validated information. From primary prevention to survivorship and end of life issues, communication empowers people to make informed cancer-related decisions and to engage in behaviors that will improve their health.

To build on our progress in refining health communication theories and interventions, we must close major gaps in our understanding of how people access and use health information as well as the gaps between what is known and what is practiced. We must:

- Provide accurate and balanced information about all areas of cancer prevention, diagnosis, treatment, and care, including complementary and alternative therapies.
- Learn how to help people distinguish important health risks from insignificant ones and make informed choices despite exposure to contradictory or inaccurate health messages.
- Inform physicians, nurses, and other health care providers of emerging best practices, help them become more effective communicators, and integrate cancer communications into all aspects of cancer care.
- Find and implement the best ways to disseminate research results to the cancer research community, medical practitioners, patients, at-risk persons, and the public.
- Increase patient access to and participation in high quality clinical trials to speed the pace of discovery.
- Reduce cancer-related health disparities through health communications research and activities.
- Expand the cadre of health communications scientists and practitioners who conduct research and apply results.

Through these efforts, we will gain a far richer understanding of how people use health information and access communications technologies of all kinds. We will use that understanding to improve outcomes in cancer prevention, early detection, and treatment, and to improve the lives of cancer survivors and those patients receiving palliative care.

Progress in Pursuit of Our Goal

The following are descriptions of major activities related to the objectives of the Extraordinary Opportunity in Cancer Communications.

Collecting and Analyzing Audience Data

To maximize the effectiveness of all our communications and to support communications research, planning, implementation, and evaluation, we are taking steps to collect, more effectively analyze, and disseminate critical information about various audience groups.

- Planning for the **Health Information National Trends Survey (HINTS)** of 9,000 participants is well underway. HINTS, to be launched in 2002, will be the only national survey focused on cancer communications. It will gather information on health, sociodemographics, and access to health care; knowledge about cancer; risk perceptions; cancer-related behaviors such as cancer prevention and screening; as well as data on such topics as personal cancer experience, social ties, and self-efficacy. The data will be analyzed and made quickly available to the research community to inform future communications research and program planning for cancer as well as other health issues. Data will also be shared with the advocacy community through briefings and special reports.

- NCI staff are tapping a health/lifestyle information database to identify and disseminate data on the information needs of specific audiences, develop appropriate educational messages, and identify the best media, locations, and techniques for communicating cancer information. Moreover, staff have developed and maintain a NewMediacy listserv that is narrowing the knowledge gap between the private and public sectors.

Increasing Access to and Use of Cancer Communications by All Populations

Pilot projects and educational materials focus on understanding and bridging the digital divide and promoting the benefits of clinical trials.

- Last year, NCI announced a new initiative and, within the same fiscal year, funded four research and development projects to develop **unique approaches for overcoming the cancer digital divide** by providing underserved groups with access to computers and the wealth of cancer information now available through computers. Each project involves public-private partnerships, and one has resulted in a joint effort with the Markle Foundation for continued funding. (See the sidebar on this page for more information.)

- Research is underway to improve and assess the communication of risks, benefits, and

other essential elements of the informed consent and decision making processes.

- A Web-based educational program is assisting research teams with issues related to the protection of human participants in research. (http://cme.nci.nih.gov, http://ohsr.od.nih.gov/cbt/)

- Our new **Cancer Clinical Trials Education Series** provides clinical trials information to the public, health care professionals, and patient groups. (See page x, Clinical Trials Challenge chapter.)

Accelerating Research and Development of Interventions

NCI has taken several steps to address the need for more focused interdisciplinary studies in cancer communications.

- We solicited applications for grants to create up to five **Centers of Excellence in Cancer Communications Research** in Fiscal Year 2002. The response was excellent, showing that this initiative meets a real need in the research community. The Centers are expected to accelerate scientific developments in cancer communications, increase the number of investigators from a range of disciplines who focus on the study of cancer communications, and train interdisciplinary investigators to conduct cutting-edge communications research directly relevant to the context of cancer prevention, detection, treatment, control, and survivorship. (http://cancercontrol.cancer.gov/communicationcenters)

- NCI also supported a Community Clinical Oncology Program project based at the University of Rochester to collect data from newly diagnosed cancer patients to learn more about their special communication needs. This information will be used for program planning and to assess the need for additional research.

Developing Communication Choices to Meet the Needs of All Users

Through the use of technology and in response to various needs, we have improved existing communication channels and developed new ones.

- NCI **World Wide Web sites have been enhanced** with an instant messaging service to answer cancer questions submitted online (http://cancer.gov/Livehelp/vp/vp_cq.html), a natural language search system, the online NCI Publications Locator (http://cissecure.nci.nih.gov/ncipubs/), and new minimum standards for improved navigability, consistency, and usability (http://usability.gov/).

- Research organizations, medical professionals, and commercial vendors are using NCI-

provided tools – a glossary that supports the "**define terms on this page**" function, for example – to enhance their ability to communicate cancer information on the World Wide Web.

- New resources enhance the effectiveness and reach of cancer communications. An online repository of NCI-cleared core information facilitates responses to inquiries from the media, public, and other sources. A new **Communication Technologies Research Center** for usability testing, technology evaluation and demonstration, and training provides the tools needed to design evidence-based cancer information products and services, and a new Emerging Technologies Unit searches out and applies new and evolving technologies to cancer communications.

- Plans are in place to ensure access to cancer information for people with limited English proficiency. These include conducting an assessment of public and private initiatives that target low-literacy issues and developing an NCI strategic approach that links these efforts to the NCI Office for Reducing Cancer-Related Health Disparities.

Science of Dissemination and Dissemination of Science

Several activities illustrate our commitment to improving dissemination of NCI research results. We are working to heighten researchers' understanding about the needs of end users of research products. We are increasing the usefulness of the products so they will benefit people. And we have put in place several mechanisms to assist scientists in the dissemination of research findings.

- To increase the likelihood that citizens will benefit from our investment in research, we are strengthening NCI's partnerships with voluntary health organizations, HMOs, and community organizations, and are planning to fund in 2002 six to eight competitive supplements to NCI grantees with effective cancer control interventions ready for dissemination.

- We are convening, in collaboration with private organizations and other Federal agencies, an interdisciplinary group to develop recommendations for intervention researchers and encourage new partnerships among researchers, funders, and receptor organizations.

- As one component of a novel partnership with the National Institute on Drug Abuse and the Robert Wood Johnson Foundation (RWJF) for the Transdisciplinary Tobacco Use Research Centers (TTURCs), RWJF has funded efforts to assure that research findings are communicated quickly to relevant health professionals and organizations and to the public. Through RWJF funding, each TTURC hired a communications specialist to facilitate communication with the public, researchers, and the media. This is a unique component of these grants. (Cross-reference with Tobacco Extraordinary Opportunity.)

- In partnership with the Agency for Healthcare Research and Quality (AHRQ), we have commissioned an evidence-based review of effective strategies to facilitate dissemination of cancer-related interventions. We will communicate the results through the World Wide Web, print, and other channels.

- In partnership with the Centers for Medicare and Medicaid Services, we are helping to support a national demonstration to test a new Medicare smoking cessation benefit for older smokers, including dissemination of an evidence-based smoking cessation guide for smokers ages 50 and older and a guide for Spanish-speaking Medicare beneficiaries.

- In partnership with AHRQ, we are conducting syntheses of the research in a number of areas, such as dietary behavior interventions, decision aids, and dissemination.

Raising the Visibility and Prominence of Cancer Communications

In 2000, NCI established the Eleanor Nealon Extraordinary Communicators Lecture and Award Series to pay tribute to outstanding communicators. Awardees speak about their personal and professional experiences and are recognized in a public ceremony on the NIH campus.

NCI Education and Communications Products (sidebar or highlighted block)

New NCI education and communications products serve as essential tools for researchers, patients, and health care providers. Recent products include:

- Report of an evidence review of cancer-related decision aids funded through the Agency for Healthcare Research and Quality (http://www.ahrq.gov/)
- *Understanding Cancer Pain* series, developed in collaboration with Johns Hopkins Oncology Center (http://oesi.nci.nih.gov/Understanding_Cancer_Pain/)
- A searchable *Risk Communication Bibliography* (http://cancercontrol.cancer.gov/DECC/riskcommbib/)
- *Efficacy of Interventions To Modify Dietary Behavior Related to Cancer Risk* (http://www.ahrq.gov/clinic/dietsumm.htm)
- *5 A Day for Better Health Program Evaluation Report* (http://cancercontrol.cancer.gov/5ad_exec.html)
- A *pamphlet for the general public on environmental cancers*, developed in collaboration with the National Institute of Environmental Health Sciences and the National Toxicology Program
- Materials on the Web and in print to inform seniors and people with disabilities about Medicare's new policy to provide coverage for clinical trials, developed through a partnership with the Centers for Medicare and Medicaid Services

(http://cancertrials.nci.nih.gov/researchers, http://cis.nci.nih.gov/fact/8_14.htm)

- A new cancer survivorship series, developed through a partnership with the National Coalition for Cancer Survivorship
- A booklet on genetic testing to help people at risk for inherited cancers and those who perceive themselves at risk decide whether to explore genetic counseling and testing for cancer susceptibility (http://oesi.nci.nih.gov/GENBRST/INDEX.HTM)
- A booklet to improve the way people think about and make use of data in health decision making.

Recent Research Findings Related to Cancer Communications (sidebar or highlighted block)

Digital Divide Pilot Projects. NCI is supporting four research and development projects to overcome the digital divide by testing the efficacy of new communications technologies in cancer prevention and education. These projects involve partnerships among NCI-supported Cancer Centers and Cancer Information Service (CIS) Centers at universities and a wide range of community organizations and programs including Head Start, urban and rural community groups, senior centers, and computer suppliers. We will assess the results of the pilot projects and disseminate information about promising interventions.

- The New England regional CIS office and the Yale University Cancer Center are partnering with a Head Start Center, a group concerned with urban policy, and a group that supplies computers to children to develop techniques for teaching Head Start parents how to use computers and access health information on the Web.
- The Memorial Sloan Kettering Cancer Center and the New York State regional CIS office are partnering to increase access to cancer information and the use of technology by residents of an economically depressed area in the community.
- The University of Wisconsin and the North Central and Mid-West CIS offices are collaborating to promote the use of, and training by peer advocates for, a computer-based education program among underserved women diagnosed with breast cancer in a rural area in one state and an urban area in another. The project is helping some 280 African American women in the urban area play a larger role in their own care by providing them with access to online information. They are being trained in the use of laptop computers and are learning to get cancer information and support over the World Wide Web. These patients say it helps them connect with people and information at all hours of the day and night, especially when they are worried.
- A collaboration between Louisiana State University and the Mid-South regional office of the CIS is examining the use of a low-literacy cancer information computer program to determine its potential to increase the use of new communication technologies for health information by older adults in a group of senior centers.

(For more information, go to http://cancercontrol.cancer.gov/eocc/ddpp.html.)

Study Shows Perceptions Can Change. NCI-supported researchers have shown that the combination of tailored print materials and a call from a telephone health advisor can have several positive effects. This was the first study to show that women's perceived risks about breast cancer could be changed, and that the changes were maintained a year later. Women who received the combination of tailored communications also were more knowledgeable about breast cancer and mammography and were significantly more likely to get mammograms.

Research on Targeted and Tailored Communications Highlights Successes. A group of NCI-sponsored health communications researchers recently teamed up to prepare articles for a special issue of the *Journal of Family and Community Health*. They reported on their efforts to develop communications for special populations, such as Asians, African Americans and Hispanics, and to individualize cancer information. One team showed that focus groups could be conducted through the Internet and therefore could include people who would not otherwise participate. Another group tested the feasibility of a tailored, interactive computerized cancer pain program for patients. In pilot research, the majority of patients said the computer programs were easy, enjoyable, and informative tools. The computer programs extend the reach of health professionals and permit better reporting of patients' pain and tailored advice based on the patient's unique pain profile.

The Plan – Cancer Communications

Goal

Increase knowledge about, tools for, access to, and use of cancer communications by the public, consumers, patients, survivors, and health professionals – with a special focus on diverse populations – to accelerate reductions in the U.S. cancer burden.

Objectives and Milestones for Fiscal Year 2003

1. **Establish new data collection and analysis strategies to support cancer communications planning and evaluation.**

- Analyze data from the Health Information National Trends Survey (HINTS) and make results available to researchers and program planners as early as possible.
- Explore the use of Internet-based data collection to follow a subset of people interviewed as part of HINTS.[9]
- Conduct a HINTS survey of cancer survivors in parallel with the HINTS public survey. The HINTS-S, or HINTS survivors survey, will collect data on survivors' use of different media, their risk perceptions, cancer-related behaviors, personal cancer experiences, and use of complementary and alternative medicine. We will assure adequate representation of diverse population groups.
- Explore the need for national data collection about health professionals' communication practices.
- Continue to operate the NewMediacy listserv and health and lifestyle database to inform NCI's planning and evaluation efforts about which audiences use which new media, and how they use them.
- Create a searchable database of cancer-related communication research reports accessible to researchers and program planners.

2. **Increase access to and use of cancer communications by all populations, especially underserved populations.**

- Analyze and disseminate results of four Digital Divide Pilot Projects to test strategies to increase access to and use of online and other interactive cancer communications by underserved populations.
- Fund additional Digital Divide Pilot Projects and evaluate outcomes.
- Transform the clinical trials Web portal to enable visitors to more quickly find information and resources.

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[9] It is becoming increasingly difficult, especially in major U.S. cities, to conduct telephone interviews. With the rapid penetration of the Internet and the fact that the demographics of the Internet are becoming more like the U.S. population, it is time to assess the feasibility of collecting HINTS data through Internet-based interviews. Ultimately, such methods might be more appealing to people being interviewed since they could complete surveys at their convenience. We also will explore the addition of non-invasive biospecimens to complement the interview data for Internet-based surveys.

3. **Accelerate the pace of research and development of interventions in cancer communications.**

- Continue to support Centers of Excellence in Cancer Communications Research.
- Establish interdisciplinary training partnerships and fund health communications laboratories to develop and conduct training programs for researchers in growing areas, including risk communications and interactive health communications.

4. **Develop a menu of communication choices to meet the needs of all users, and especially to increase knowledge about, tools for, access to, and use of these choices by diverse populations.**

- Develop new tools and products to facilitate cancer communications for the public, patients and their caregivers, underserved populations, advocacy groups, health professionals, and cancer communicators.
- Continue work with Agency for Healthcare Research and Quality to fund research on decision aids ("Making Quality Count for Consumers and Patients"). Link with Digital Divide Pilot Projects to promote dissemination and use of interactive communication tools, and collect information on current levels of, and barriers to, use.
- Assess the status of low-literacy research and national initiatives in order to develop a strategic plan for low-literacy programs and materials.
- Develop and promote a media toolkit to facilitate the media's use of NCI's resources in preparing cancer-related stories.

5. **Improve the science of dissemination and the dissemination of science to assure that our citizens realize the benefits of research investments.**

- Fund dissemination and diffusion supplements to grantees with proven interventions ready for dissemination.

The Changing Scene for Cancer Communications (sidebar or highlighted block)

Changes in the role and accessibility of information are altering health care practices, patient-physician relationships, and the way consumers and patients acquire and use information:

In January 2001, 162 million people (58 percent of the U.S. population) accessed the Internet from home. (Nielsen//Net Ratings, February 2001)

The majority of Internet users have looked for medical and health information online.

- About 57 percent have gone online to get medical information. (Pew Internet and American Life Project, February 2001)
- Some percent of all online adults use the Internet to look for health care information; 24 percent go directly to a site that focuses only on health-related topics. (Harris Interactive, April 2001)

Approximately 55 percent of physicians use e-mail to communicate with colleagues; 13percent use it to communicate with their patients. (Harris Interactive, February 2001)

More and more patients want to communicate with their physicians via the Internet.

- 81 percent of online adults would like to receive e-mail reminders for preventive care.
- 83 percent would like follow-up e-mails after doctor visits.
- 84 percent would like their doctors to be able to access and monitor their lab tests online.

(Harris Interactive, January 2001)

Health insurers increasingly offer online patient-doctor consultations and reimburse doctors for their time. (Gannett News Service, April 23, 2001)

In 2000, the Association of Cancer Online Resources (ACOR) delivered nearly 2 million individual e-mails weekly to cancer survivors, their loved ones, health care professionals, and members of the public who participate in ACOR's online services. (ACOR, April 2001).

Planning National Agendas for Disease-Specific Research

Each of the 1,268,000 Americans who will be diagnosed with cancer this year will battle a very specific, very personal disease. While the hundred-plus distinct diseases we call "cancer" have several essential attributes in common, each type of cancer has its own unique characteristics that affect how it arises, how it progresses, and how it can be most effectively treated. And while we have learned much that is broadly applicable to cancer through our core research programs and the initiatives of the Extraordinary Opportunities, we must be equally alert to the specific tendencies and behaviors of each cancer type. This is why NCI plans, promotes, and carries out an ambitious program of *disease-specific research*.

NCI charts the course for its disease-specific efforts primarily through advice from expert Progress Review Groups (PRGs). The PRGs are panels of 20 to 30 prominent members of the scientific, medical, and advocacy communities that assess the state of the science for a single type of cancer or a group of closely related cancers and make recommendations for future research. Over a nine-month period, each PRG identifies gaps in our understanding of the disease under study, barriers to progress, and key research priorities. The process culminates in the wide release of PRG findings and priorities in a comprehensive report. All PRG reports become road maps that guide NCI and the scientific community in their efforts to make progress against specific types of cancer. To date, six PRG reports have been issued. Six more PRGs are in progress or planned. (See schedule, page xx.)

NCI's extensive slate of PRGs includes breast, prostate, lung, and other common types of cancer as well as less common diseases like pancreatic cancer, multiple myeloma, and brain tumors. By addressing these more unusual types of cancer through the PRGs, NCI hopes to raise awareness of the scientific opportunities afforded by each disease and to stimulate much-needed research.

Response and Communication

NCI responds rapidly and enthusiastically to PRG recommendations. For each PRG, NCI staff:

- Form an internal working group of disease-specific experts to spearhead the Institute's response to the recommendations, identify gap in our understanding, and propose new programs and initiatives where needed.
- Thoroughly analyze the recommendations to determine the extent to which they are being addressed – or could be addressed – through existing programs or efforts.
- Reconvene the PRG to discuss what we learn through this analysis and to clarify what gaps remain.
- Develop strategies to implement the recommendations, particularly in gap areas.
- Communicate our decisions to the scientific community and enlist their active

participation in the implementation process.
- Ensure that effective mechanisms are in place to implement decisions.
- Follow up to ensure that the recommendations continue to be addressed.
- Report on our results.

To ensure that researcher and advocacy communities are aware of NCI's disease-specific priorities, NCI is developing a comprehensive plan for disseminating the PRG reports. PRG-related information is distributed at major medical meetings, in journals and newsletters, and on the World Wide Web. NCI has also partnered with several advocacy groups to promote the priorities identified by various PRGs.

Even with all these efforts in place, we recognize that the ultimate success of the PRG process depends on researchers' ability and willingness to undertake research projects in disease-specific areas of critical need. NCI encourages the scientific community to respond to its disease-specific priorities by treating the PRG reports as broad Program Announcements that indicate the most pressing needs and opportunities. Grant applications that reference a PRG report receive special consideration in the funding exceptions process. (For more on the exceptions process, see page xxx.)

Consumer advocates also play a key role in the PRGs and their follow-up. Advocates are involved throughout the PRG process, keeping their communities informed about the PRG and its recommendations and mobilizing in support of PRG priorities. They may also help raise awareness of the priorities among researchers and clinicians.

Highlights of PRG Recommendations

Based on review and analysis of the recommendations of the first six PRGs, it is clear that many of the recommendations are, or could potentially be, addressed by programs that are already in place. In some cases modification or supplementation of an existing program is sufficient to get the research on track. The PRGs have also pointed to obvious gaps in NCI's disease-specific programs. For example:

- The *Breast Cancer PRG* noted that our lack of understanding of the biology and developmental genetics of the normal breast was a significant barrier to progress against the disease. The NCI responded by joining several other NIH Institutes to release a Program Announcement (PA) seeking applications for research on normal breast development, as well as on changes in the breast throughout the development of early and advanced cancer. This PA has generated eight new research projects.
- The *Prostate Cancer PRG* told us that the lack of validated animal models of prostate cancer was severely impeding progress. Since then, four separate research teams have begun work on models of prostate cancer through NCI's Mouse Models of Human Cancers Consortium.
- The *Leukemia, Lymphoma, and Myeloma PRG* found that the infrastructure for new treatments of hematologic malignancies, particularly those exploiting molecular targets, is

inadequate. They called for the development of consortia that would bring together experts across multiple disciplines and institutions to participate in the rapid discovery and development of cancer therapies. The ultimate goal of the program would be to shorten drug development time of five to ten years to about two years through an alliance among academia, industry, government, and patients. NCI is currently investigating ways to create and support these novel consortia.

Furthermore, NCI is taking steps to address a number of broad scientific needs noted by several PRGs, such as the need for research training and the development of biomarkers of disease. For example:

- NCI is currently expanding the *Specialized Programs of Research Excellence (SPOREs)* program to cover a number of the cancers addressed by the PRGs, including gynecologic cancers, brain tumors, leukemia, lymphoma, and myeloma. SPOREs are described in detail on page [xx].
- Several PRGs have recognized a need for the identification of biomarkers of disease. The *Early Detection Research Network (EDRN)* is dedicated to meeting this need. Projects specifically related to prostate, lung, and ovarian cancers are among those well under way, with others planned. For more on EDRN, see page xx.

Several PRGs discussed the importance of more accurate diagnosis and staging of cancer. Research conducted through the *The Director's Challenge: Toward a Molecular Classification of Tumor* will facilitate diagnosis at the molecular level, enabling greater precision in diagnosis and treatment. To date, the Director's Challenge has stimulated some 22 supported projects covering a diverse array of cancers including lung, colon, and prostate cancers, brain tumors, and osteosarcoma. See page xx for more information on the Director's Challenge initiative.

Are the PRGs making a clear difference in scientific research and discovery?

It is too early to fully assess this but the early signs are encouraging. NCI has recently begun the critical task of assessing the impact of the PRG effort within the research community. As part of a system for evaluating the PRG process and outcomes, the Institute will analyze changes in funding levels, types of research funded, and grant application response that occur after the completion of a PRG. Starting with the Breast and Prostate PRGs, NCI will issue a status report two to three years after each PRG, and the groups will reconvene to discuss the status of the recommendations and NCI's response and to recommend further action. This process will provide valuable information and insight about our directions in disease-specific planning.

While the process may be refined over time, it is clear that the combined perspectives of PRG members, NCI staff, researchers, and cancer advocates will continue to have a synergistic impact on the future direction of both broad-based and disease-specific research. By working together, we can ensure the most effective use of resources focused on both needs

and opportunities for advances against all cancers.

How It All Comes Together - to be added

A brief example of how the elements of the plan fit together to address questions in cancer prevention, detection and diagnosis, treatment, etc.

Features – more to be added

People's stories, Spotlights on research, etc.

Mouse Models of Human Cancers Consortium – Modeling Human Cancers in the Mouse

Animal models – laboratory animals that have specific characteristics resembling a human disease or disorder – play an invaluable role in cancer research. Technologies available today allow scientists to create animal models of cancer by transferring new genes into animals or inactivating certain existing genes. This makes the animals susceptible to specific cancers via the same genetic and environmental factors that affect humans. With these models, scientists can study the biological changes associated with every stage of tumor development, test new approaches to detection and diagnosis, and evaluate prevention and treatment strategies.

For a variety of reasons, mice are particularly well suited for cancer research. To start, mice and humans are similar in their genetic makeup and susceptibility to cancer. As a result, the development of tumors in mice largely parallels that in humans. Further, mouse tumors develop over the course of months rather than the years usually required for cancer to develop in larger animals and humans.

But the complexity of cancer makes the development of mouse models a far more challenging task for cancer than for some other diseases. Fortunately, cancer researchers today have a wide range of resources to bring to bear on this task. Scientists have access to increasingly detailed databases containing the details of mouse and human genes and a growing body of information on the molecular characteristics, or *signatures*, of tumors. This expanding knowledge – coupled with tools for modifying the genes of laboratory mice and a battery of tests to identify relevant cancer genes and proteins – ensure that cancer mouse models parallel the development, progression, and clinical course of human cancers.

To improve the pace and efficiency with which mouse models of cancer are developed and tested, and to ensure they are readily available to scientists, NCI created the **Mouse Models of Human Cancers Consortium** in late 1999 by funding 20 multidisciplinary groups of investigators. Consortium scientists are working to develop and evaluate mouse models for breast, prostate, lung, ovary, cervix, pancreas, skin, blood and lymph system, colon, and brain cancers.

How Mouse Models Are Advancing Cancer Research

Throughout the Consortium and in other NCI-supported laboratories, researchers are using mouse models to do the following: examine the interplay of genetic and environmental factors in cancer susceptibility; test novel approaches to detection, diagnosis, and imaging; and advance the use of genetically engineered mice for prevention, therapy, and population research.

Mouse models provide a unique opportunity to **explore how genetic and environmental factors interact** to give rise to cancer. With such models, scientists can test the effects of a particular chemical in a controlled environment using animals with a known genetic makeup. For example, researchers are using a recently developed mouse model of lung cancer to investigate the role that genetic factors play in determining why some smokers develop lung cancer and others do not. The model also is being used to test whether tobacco smoke accelerates tumor formation, and to define the genes that confer susceptibility to tobacco-related cancers.

Because samples of human cancers at their earliest stages can be difficult to obtain, mouse models also are **invaluable in cancer detection studies**. Tumors in these mice can be examined to verify the role that each genetic alteration plays in causing cancer and in its progression, and may also reveal changes informative to human cancer diagnosis or early detection. An example of this type of research is a newly developed mouse model that closely mimics inflammatory bowel disease, a condition associated with increased cancer risk. Researchers are using this model to test the effect of known and suspected causal factors – such as the Helicobacter bacteria – on the timing and severity of cancer. By taking biopsies at varying times after infection, they are looking for the earliest changes indicating increased risk for gastric, intestinal, or colon cancer.

Defining the changes associated with cancer is fundamental for successful early detection, as well as for finding potential targets for early intervention. Once these targets have been identified, scientists depend on mouse models to **test the efficacy of new drugs**, and to **understand why a drug does – or does not – work as expected**. Indeed, one of the most important roles of mouse models is in the development of drugs to treat cancer.

In one recent example of using mouse models to **test treatments**, investigators used a model of one type of childhood leukemia to help solve the mystery of why some children respond to the standard therapy of retinoids while others do not. As they studied the problem in the model, scientists discovered that the mice that did not respond to treatment had an unexpected gene rearrangement. With this information, the researchers then developed a new treatment that blocks the action of the rearranged gene. It was effective in combination with retinoids in mice, and these investigators are now assessing the combined treatment in childhood leukemia patients who do not respond to retinoid therapy alone. Models also are valuable for **studying a host of treatment questions**, such as determining mechanisms of drug resistance and defining new treatment targets.

With specialized equipment and techniques for imaging mice and other small animals, investigators are using mouse models to **explore improvements in cancer imaging and treatment** in order to determine whether anti-cancer drugs have reached their targets and to track response to therapy. Since 1999, much of this research has been fostered by Small Animal Imaging Resource Programs that NCI has established at a number of research centers around the country. (See page x for more information.)

As Consortium investigators develop more mouse models of cancer, collaborations between

them and small animal imaging specialists are expected to grow. Already, Consortium scientists involved in developing mouse models for prostate cancer have teamed with colleagues from the NCI-funded Small Animal Imaging Resource Program to use positron emission tomography imaging to study prostate cancer development, from its beginnings in the prostate to its metastasis (spread) to bones and other organs. Similarly, investigators testing mouse models of brain tumors are collaborating with small animal imaging experts to use magnetic resonance imaging to test approaches to gene therapy for brain tumors. Experiments of this kind are already revealing new avenues for human therapy.

The Future of Mouse Models

If the research community is to employ mouse models to their greatest advantage, extensive collaborations are needed among those who can best inform the design of the models and their ultimate use in cancer research. NCI is facilitating the formation of collaborative groups – e.g., for ovarian, brain, pediatric, and pancreatic cancer modeling – to ensure rapid incorporation of human cancer research discoveries into mouse model design and application. With NCI's help to organize conferences and symposia, Consortium investigators are spearheading the dissemination of information about mouse engineering tactics, development of validation standards for cancer models, and the practical application of models to inform many aspects of cancer research.

The achievements of Consortium investigators and the need to deploy models to the research community prompted NCI to establish the Mouse Models of Human Cancers Consortium Mouse Repository (http://web.ncifcrf.gov/researchresources/mmhcc/default.asp), to which interested scientists are invited to contribute models. When it opened in February 2001, the NCI repository had three mouse strains available for distribution. The number of mouse models offered is expected to quickly increase, reaching at least 30 by early 2002. NCI will expand the repository in the future to accommodate the growing requirements of the cancer research community for well-designed and thoroughly tested mouse models. For more information about Consortium programs and projects, and access to its databases, go to http://mmhcc.nci.nih.gov/.

Story of Discovery - to be added

A narrative and graphic depiction of the 40 years of research and development that led to development and recent approval of the drug STI-571 (Gleevec) for the treatment of chronic myelogenous leukemia.